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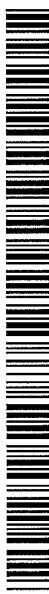
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[Continued on next page]

(54) Title: STILBENE DERIVATIVES AND THEIR USE FOR BINDING AND IMAGING AMYLOID PLAQUES

(57) **Abstract:** This invention relates to a method of imaging amyloid deposits and to labeled compounds, and methods of making labeled compounds useful in imaging amyloid deposits. This invention also relates to compounds, and methods of making compounds for inhibiting the aggregation of amyloid proteins to form amyloid deposits, and a method of delivering a therapeutic agent to amyloid deposits.



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STILBENE DERIVATIVES AND THEIR USE FOR BINDING AND IMAGING AMYLOID PLAQUES

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to novel bioactive compounds, methods of diagnostic imaging using radiolabeled compounds, and methods of making radiolabeled compounds.

Background Art

[0002] Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, irreversible memory loss, disorientation, and language impairment. Postmortem examination of AD brain sections reveals abundant senile plaques (SPs) composed of amyloid- β (A β) peptides and numerous neurofibrillary tangles (NFTs) formed by filaments of highly phosphorylated tau proteins (for recent reviews and additional citations see Ginsberg, S. D., *et al.*, "Molecular Pathology of Alzheimer's Disease and Related Disorders," in *Cerebral Cortex: Neurodegenerative and Age-related Changes in Structure and Function of Cerebral Cortex*, Kluwer Academic/Plenum, NY (1999), pp. 603-654; Vogelsberg-Ragaglia, V., *et al.*, "Cell Biology of Tau and Cytoskeletal Pathology in Alzheimer's Disease," *Alzheimer's Disease*, Lippincot, Williams & Wilkins, Philadelphia, PA (1999), pp. 359-372). Familial AD (FAD) is caused by multiple mutations in the A precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes (Ginsberg, S. D., *et al.*, "Molecular Pathology of Alzheimer's Disease and Related Disorders," in *Cerebral Cortex: Neurodegenerative and Age-related Changes in Structure and Function of Cerebral Cortex*, Kluwer Academic/Plenum, NY (1999), pp. 603-654; Vogelsberg-Ragaglia, V., *et al.*, "Cell Biology of Tau and Cytoskeletal Pathology in Alzheimer's Disease,"

Alzheimer's Disease, Lippincot, Williams & Wilkins, Philadelphia, PA (1999), pp. 359-372).

[0003] While the exact mechanisms underlying AD are not fully understood, all pathogenic FAD mutations studied thus far increase production of the more amyloidogenic 42-43 amino-acid long form of the A β peptide. Thus, at least in FAD, dysregulation of A β production appears to be sufficient to induce a cascade of events leading to neurodegeneration. Indeed, the amyloid cascade hypothesis suggests that formation of extracellular fibrillar A β aggregates in the brain may be a pivotal event in AD pathogenesis (Selkoe, D. J., "Biology of B-amyloid Precursor Protein and the Mechanism of Alzheimer's Disease," *Alzheimer's Disease*, Lippincot Williams & Wilkins, Philadelphia, PA (1999), pp. 293-310; Selkoe, D. J., *J. Am. Med. Assoc.* 283:1615-1617 (2000); Naslund, J., *et al.*, *J. Am. Med. Assoc.* 283:1571-1577 (2000); Golde, T. E., *et al.*, *Biochimica et Biophysica Acta* 1502:172-187 (2000)).

[0004] Various approaches in trying to inhibit the production and reduce the accumulation of fibrillar A β in the brain are currently being evaluated as potential therapies for AD (Skovronsky, D. M. and Lee, V. M., *Trends Pharmacol. Sci.* 21:161-163 (2000); Vassar, R., *et al.*, *Science* 286:735-741 (1999); Wolfe, M. S., *et al.*, *J. Med. Chem.* 41:6-9 (1998); Moore, C. L., *et al.*, *J. Med. Chem.* 43:3434-3442 (2000); Findeis, M. A., *Biochimica et Biophysica Acta* 1502:76-84 (2000); Kuner, P., Bohrmann, *et al.*, *J. Biol. Chem.* 275:1673-1678 (2000)). It is therefore of great interest to develop ligands that specifically bind fibrillar A β aggregates. Since extracellular SPs are accessible targets, these new ligands could be used as *in vivo* diagnostic tools and as probes to visualize the progressive deposition of A β in studies of AD amyloidogenesis in living patients.

[0005] To this end, several interesting approaches for developing fibrillar A β aggregate-specific ligands have been reported (Ashburn, T. T., *et al.*, *Chem. Biol.* 3:351-358 (1996); Han, G., *et al.*, *J. Am. Chem. Soc.* 118:4506-4507 (1996); Klunk, W. E., *et al.*, *Biol. Psychiatry* 35:627 (1994); Klunk, W. E., *et al.*, *Neurobiol. Aging* 16:541-548 (1995); Klunk, W. E., *et al.*, *Society for Neuroscience Abstract* 23:1638 (1997); Mathis, C. A., *et al.*, *Proc. XIIth Int'l.*

Symp. Radiopharm. Chem., Uppsala, Sweden:94-95 (1997); Lorenzo, A. and Yankner, B. A., *Proc. Natl. Acad. Sci. U.S.A.* 91:12243-12247 (1994); Zhen, W., et al., *J. Med. Chem.* 42:2805-2815 (1999)). The most attractive approach is based on highly conjugated chrysamine-G (CG) and Congo red (CR), and the latter has been used for fluorescent staining of SPs and NFTs in postmortem AD brain sections (Ashburn, T. T., et al., *Chem. Biol.* 3:351-358 (1996); Klunk, W. E., et al., *J. Histochem. Cytochem.* 37:1273-1281 (1989)). The inhibition constants (K_i) for binding to fibrillar $\text{A}\beta$ aggregates of CR, CG, and 3'-bromo- and 3'-iodo derivatives of CG are 2,800, 370, 300 and 250 nM, respectively (Mathis, C. A., et al., *Proc. XIIth Intl. Symp. Radiopharm. Chem., Uppsala, Sweden*:94-95 (1997)). These compounds have been shown to bind selectively to $\text{A}\beta$ (1-40) peptide aggregates *in vitro* as well as to fibrillar $\text{A}\beta$ deposits in AD brain sections (Mathis, C. A., et al., *Proc. XIIth Intl. Symp. Radiopharm. Chem., Uppsala, Sweden*:94-95 (1997)).

[0006] Amyloidosis is a condition characterized by the accumulation of various insoluble, fibrillar proteins in the tissues of a patient. An amyloid deposit is formed by the aggregation of amyloid proteins, followed by the further combination of aggregates and/or amyloid proteins. Formation and accumulation of aggregates of β -amyloid ($\text{A}\beta$) peptides in the brain are critical factors in the development and progression of AD. The fibrillar aggregates of amyloid peptides, $\text{A}\beta_{1-40}$ and $\text{A}\beta_{1-42}$, are major metabolic peptides derived from amyloid precursor protein found in senile plaques and cerebrovascular amyloid deposits in AD patients (Xia, W., et al., *J. Proc. Natl. Acad. Sci. U.S.A.* 97:9299-9304 (2000)). Prevention and reversal of $\text{A}\beta$ plaque formation are being targeted as a treatment for this disease (Selkoe, D., J. *JAMA* 283:1615-1617 (2000); Wolfe, M.S., et al., *J. Med. Chem.* 41:6-9 (1998); Skovronsky, D.M., and Lee, V.M., *Trends Pharmacol. Sci.* 21:161-163 (2000)).

[0007] In addition to the role of amyloid deposits in Alzheimer's disease, the presence of amyloid deposits has been shown in diseases such as Mediterranean fever, Muckle-Wells syndrome, idiopathic myeloma, amyloid polyneuropathy, amyloid cardiomyopathy, systemic senile amyloidosis,

amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Down's syndrome, Scrapie, Creutzfeldt-Jacob disease, Kuru, Gerstamnn-Straussler-Scheinker syndrome, medullary carcinoma of the thyroid, Isolated atrial amyloid, β_2 -microglobulin amyloid in dialysis patients, inclusion body myositis, β_2 -amyloid deposits in muscle wasting disease, and Islets of Langerhans diabetes Type II insulinoma.

[0008] Thus, a simple, noninvasive method for detecting and quantitating amyloid deposits in a patient has been eagerly sought. Presently, detection of amyloid deposits involves histological analysis of biopsy or autopsy materials. Both methods have drawbacks. For example, an autopsy can only be used for a postmortem diagnosis.

[0009] Imaging agents may be based on two types of isotopes. ^{99m}Tc ($T_{1/2}$, 6 h; 140 KeV) and ^{123}I ($T_{1/2}$, 13 h; 159 KeV) are routinely used for single photon emission computed tomography (SPECT), while ^{11}C ($T_{1/2}$, 20 min; 511 KeV) and ^{18}F ($T_{1/2}$, 110 min; 511 KeV) are commonly used for positron emission tomography (PET).

[0010] The direct imaging of amyloid deposits *in vivo* is difficult, as the deposits have many of the same physical properties (e.g., density and water content) as normal tissues. Attempts to image amyloid deposits using magnetic resonance imaging (MRI) and computer-assisted tomography (CAT) have been disappointing and have detected amyloid deposits only under certain favorable conditions. In addition, efforts to label amyloid deposits with antibodies, serum amyloid P protein, or other probe molecules have provided some selectivity on the periphery of tissues, but have provided for poor imaging of tissue interiors.

[0011] Potential ligands for detecting $\text{A}\beta$ aggregates in the living brain must cross the intact blood-brain barrier. Thus brain uptake can be improved by using ligands with relatively smaller molecular size (compared to Congo Red) and increased lipophilicity. Highly conjugated thioflavins (S and T) are commonly used as dyes for staining the $\text{A}\beta$ aggregates in the AD brain (Elhaddoui, A., *et al.*, *Biospectroscopy* 1: 351-356 (1995)). These

compounds are based on benzothiazole, which is relatively small in molecular size.

[0012] It would be useful to have a noninvasive technique for imaging and quantitating amyloid deposits in a patient. In addition, it would be useful to have compounds that inhibit the aggregation of amyloid proteins to form amyloid deposits and a method for determining a compound's ability to inhibit amyloid protein aggregation.

SUMMARY OF THE INVENTION

[0013] The present invention provides novel compounds of Formula I, II, III IV or V.

[0014] The present invention also provides diagnostic compositions comprising a radiolabeled compound of Formula I, II, III, IV or V and a pharmaceutically acceptable carrier or diluent.

[0015] The invention further provides a method of imaging amyloid deposits, the method comprising introducing into a patient a detectable quantity of a labeled compound of Formula I, II, III, IV or V or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

[0016] The present invention also provides a method for inhibiting the aggregation of amyloid proteins, the method comprising administering to a mammal an amyloid inhibiting amount of a compound Formula I, II, III, IV or V or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

[0017] A further aspect of this invention is directed to methods and intermediates useful for synthesizing the amyloid inhibiting and imaging compounds of Formula I, II, III, IV or V described herein.

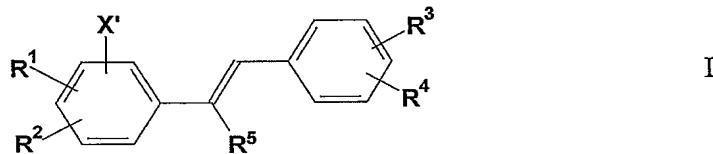
BRIEF DESCRIPTION OF THE FIGURES

[0018] FIGURES 1, 3, 4 and 5 depict representative compounds of the present invention and the binding data for these compounds.

[0019] FIG. 2 depicts the binding data for a compound of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0020] A first aspect of the present invention is directed to compounds of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R⁵ is hydrogen or C₁₋₄ alkyl;

R¹, R² and R³, in each instance, is independently selected from the group consisting of hydrogen, halogen, C₁₋₄ alkyl, cyano, carboxy(C₁₋₅)alkyl, trifluoromethyl, nitro, methylamino, dimethylamino, halo(C₁₋₄)alkyl, and formyl;

R⁴ is selected from the group consisting of:

- a. C₁₋₄ alkylthio,
- b. halo(C₁₋₄)alkoxy,
- c. carboxy(C₁₋₅)alkyl,
- d. hydroxy,
- e. C₁₋₄ alkoxy,
- f. NR⁶R⁷, wherein

R⁶ and R⁷ are hydrogen, halo(C₁₋₄)alkyl or C₁₋₄ alkyl,

- g. phenyl(C₁₋₄)alkyl,
- h. C₆₋₁₀ aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C₁₋₄)alkyl, and
- l. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄

alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

and,

X' is ¹²⁵I, ¹²³I, ¹³¹I, ¹⁸F, ¹⁸Fluoro(C₁₋₄)alkyl, [¹⁸Fluoro(C₁₋₄)alkyl]alkylamino, [¹⁸Fluoro(C₁₋₄)alkyl]amino, ⁷⁶Br, ⁷⁷Br or Sn(alkyl)₃.

[0021] Useful compounds falling within the scope of Formula I include compounds wherein R⁵ is hydrogen or C₁₋₄ alkyl. Especially useful values of R⁵ are hydrogen and methyl. The most useful value of R⁵ is hydrogen.

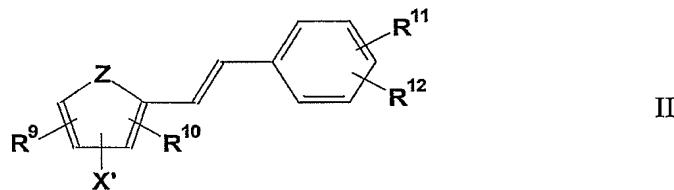
[0022] Useful compounds are those of Formula I wherein R¹, R² and R³, in each instance, is independently selected from the group as described above. Preferably, R³ is hydrogen. In this preferred embodiment, it is especially preferred that R¹ and R² are independently selected from the group consisting of hydrogen and C₁₋₄ alkyl. More preferably, at least one of R¹ and R² is hydrogen. Most preferably, R¹ and R² are hydrogen.

[0023] Useful compounds of Formula I also include those compounds wherein R⁴ is as described above. Preferable values of R⁴ under the scope of C₆₋₁₀ aryl include phenyl, naphthyl or tetrahydronaphthyl. Preferable values of R⁴ under the scope of heteroaryl include thienyl, furyl, pyranyl, pyrrolyl, pyridinyl, indolyl, and imidazolyl. Preferable values of R⁴ under the scope of heterocycle include piperidinyl, pyrrolidinyl, and morpholinyl. In compounds wherein R⁴ is a preferred embodiment of a C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl, it is most preferable that the ring is substituted with one of the following: C₁₋₄ alkylthio, carboxy(C₁₋₅)alkyl, hydroxy, methoxy, dimethylamino or methylamino. In another embodiment, R⁴ is more preferably selected from the group consisting of C₁₋₄ alkylthio, halo(C₁₋₄)alkoxy, carboxy(C₁₋₅)alkyl, hydroxy, C₁₋₄ alkoxy, and NR⁶R⁷, wherein R⁶ and R⁷ are independently hydrogen, halo(C₁₋₄)alkyl or C₁₋₄ alkyl. Most preferably, R⁴ is selected from the group consisting of methylthio, carboxymethyl, carboxyethyl, carboxypropyl, hydroxy, methoxy, or NR⁶R⁷, wherein R⁶ and R⁷ are independently hydrogen, fluoro(C₁₋₄)alkyl or methyl.

[0024] Useful values of X' include ¹²⁵I, ¹²³I, ¹³¹I, ¹⁸F, ¹⁸Fluoro(C₁₋₄)alkyl, [¹⁸Fluoro(C₁₋₄)alkyl]alkylamino, [¹⁸Fluoro(C₁₋₄)alkyl]amino, ⁷⁶Br, ⁷⁷Br or

$\text{Sn}(\text{alkyl})_3$. Especially useful values of X' are ^{123}I , ^{18}F luoromethyl, ^{18}F luoroethyl and ^{18}F luoropropyl.

[0025] The present invention is also directed to compounds of Formula II:



or a pharmaceutically acceptable salt thereof,

Z is O , S or NR^a , wherein

R^a is C_{1-4} alkyl;

R^9 , R^{10} and R^{11} , in each instance, is independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, cyano, carboxy(C_{1-5})alkyl, trifluoromethyl, nitro, methylamino, dimethylamino, halo(C_{1-4})alkyl, and formyl;

R^{12} is selected from the group consisting of:

- a. C_{1-4} alkylthio,
- b. halo(C_{1-4})alkoxy,
- c. carboxy(C_{1-5})alkyl,
- d. hydroxy,
- e. C_{1-4} alkoxy,
- f. $\text{NR}^{13}\text{R}^{14}$, wherein

R^{13} and R^{14} are hydrogen, halo(C_{1-4})alkyl or C_{1-4} alkyl,

- g. phenyl(C_{1-4})alkyl,
- h. C_{6-10} aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C_{1-4})alkyl, and
- l. C_{3-6} cycloalkyl,

wherein said phenyl(C_{1-4})alkyl, C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl is substituted with one of the following: C_{1-4}

alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

and,

X' is ¹²⁵I, ¹²³I, ¹³¹I, ¹⁸F, ¹⁸Fluoro(C₁₋₄)alkyl, [¹⁸Fluoro(C₁₋₄)alkyl]alkylamino, [¹⁸Fluoro(C₁₋₄)alkyl]amino, ⁷⁶Br, ⁷⁷Br or Sn(alkyl)₃.

Useful compounds falling within the scope of Formula II include compounds wherein Z is O, S or NR^a, wherein R^a is C₁₋₄ alkyl. Especially useful compounds are those wherein Z is O.

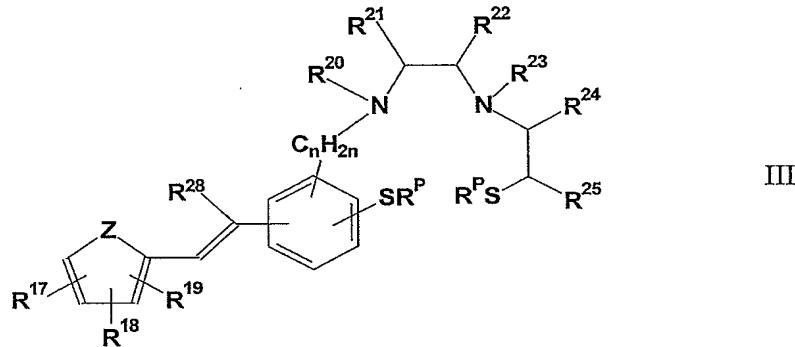
Useful compounds are those of Formula I wherein R⁹, R¹⁰ and R¹¹, in each instance, is independently selected from the group as described above. Preferably, R¹¹ is hydrogen. In this preferred embodiment, it is especially preferred that R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen and C₁₋₄ alkyl. More preferably, at least one of R⁹ and R¹⁰ is hydrogen. Most preferably, R⁹ and R¹⁰ are hydrogen.

Useful compounds of Formula I also include those compounds wherein R¹² is as described above. Preferable values of R¹² under the scope of C₆₋₁₀ aryl include phenyl, naphthyl or tetrahydronaphthyl. Preferable values of R¹² under the scope of heteroaryl include thieryl, furyl, pyranyl, pyrrolyl, pyridinyl, indolyl, and imidazolyl. Preferable values of R¹² under the scope of heterocycle include piperidinyl, pyrrolidinyl, and morpholinyl. In compounds wherein R¹² is a preferred embodiment of a C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl, it is most preferable that the ring is substituted with one of the following: C₁₋₄ alkylthio, carboxy(C₁₋₅)alkyl, methoxy, hydroxy, dimethylamino or methylamino. In another embodiment, R¹² is more preferably selected from the group consisting of C₁₋₄ alkylthio, halo(C₁₋₄)alkoxy, carboxy(C₁₋₅)alkyl, hydroxy, C₁₋₄ alkoxy, and NR¹³R¹⁴, wherein R¹³ and R¹⁴ are independently hydrogen, halo(C₁₋₄)alkyl or C₁₋₄ alkyl. Most preferably, R¹² is selected from the group consisting of methylthio, carboxymethyl, carboxyethyl, carboxypropyl, hydroxy, methoxy, or NR¹³R¹⁴, wherein R¹³ and R¹⁴ are independently hydrogen, fluoro(C₁₋₄)alkyl or methyl.

Useful values of X' include ¹²⁵I, ¹²³I, ¹³¹I, ¹⁸F, ¹⁸Fluoro(C₁₋₄)alkyl, [¹⁸Fluoro(C₁₋₄)alkyl]alkylamino, [¹⁸Fluoro(C₁₋₄)alkyl]amino, ⁷⁶Br, ⁷⁷Br or

Sn(alkyl)_3 . Especially useful values of X' are ^{123}I , $^{18}\text{Fluoromethyl}$, $^{18}\text{Fluoroethyl}$ and $^{18}\text{Fluoropropyl}$.

[0026] Another aspect of the present invention is directed to compounds of Formula III:



or a pharmaceutically acceptable salt thereof, wherein:

n is equal to a number from zero to four,

R^{28} is hydrogen or C_{1-4} alkyl,

Z is O, S or $-\text{CR}^{15}=\text{CR}^{16}-$, wherein

R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} and R^{25} in each instance, is independently selected from the group consisting of hydrogen, halogen, Sn(alkyl)_3 , C_{1-4} alkyl, C_{1-4} alkyl sulfanyl, C_{1-4} alkyl sulfonyl, C_{1-4} alkoxy, hydroxy, C_{6-10} aryl, carboxyalkyl, carboxy and $\text{NR}^{26}\text{R}^{27}$, wherein

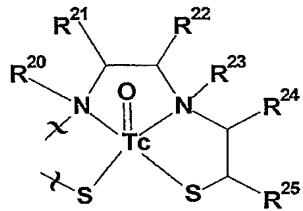
R^{26} and R^{27} are independently hydrogen, C_{1-4} alkyl, phenyl(C_{1-4})alkyl, halo(C_{1-4})alkyl, haloaryl(C_{1-4})alkyl, C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl, wherein

 said C_{6-10} aryl, C_{6-10} heteroaryl, heterocycle or C_{3-6} cycloalkyl is unsubstituted or substituted with one of the following: C_{1-4} alkylthio, C_{1-4} alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino,

and,

R^P is hydrogen or a sulfur protecting group, such as methoxymethyl, methoxyethoxymethyl, *p*-methoxybenzyl or benzyl.

[0027] The tetradentate metal ligand moiety of Formula III is capable of complexing with a metal, such as 99m -pertechnetate, as described herein to form metal chelates, exemplified by the following Formula:



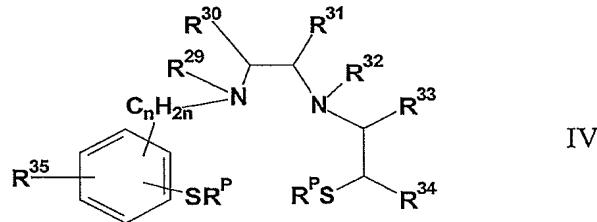
[0028] Additionally, a rhenium radioisotope can be complexed with the tetradentate metal ligand.

[0029] Useful compounds of Formula III are those compounds wherein Z is O, S or $-CR^{15}=CR^{16}-$, wherein R^{15} and R^{16} are as described above. Preferably, Z is $-CR^{15}=CR^{16}-$, wherein R^{15} and R^{16} are as described above. More preferably, R^{15} and R^{16} are hydrogen.

[0030] Useful compounds of the present invention are those compounds wherein R^{17} through R^{25} are as defined above. Preferable values of R^{17} through R^{25} falling under the scope of C_{6-10} aryl include phenyl, naphthyl or tetrahydronaphthyl. Preferable values of R^{17} through R^{25} falling under the scope of heteroaryl include thienyl, furyl, pyranyl, pyrrolyl, pyridinyl, indolyl, and imidazolyl. Preferable values of R^{17} through R^{25} falling under the scope of heterocycle include piperidinyl, pyrrolidinyl, and morpholinyl. In compounds wherein R^{17} through R^{25} are a preferred embodiment of a C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl, it is most preferable that the ring is substituted with one of the following: C_{1-4} alkylthio, C_{1-4} alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino. In another embodiment, more preferred compounds include those compounds wherein one or more of R^{17} through R^{25} is hydrogen. In this embodiment, it is preferred that R^{17} is other than hydrogen. More preferably, R^{17} is selected from the group consisting C_{1-4} alkylthio, C_{1-4} alkyl sulfonyl, hydroxy, C_{1-4} alkoxy, $NR^{26}R^{27}$, wherein R^{26} and R^{27} are independently hydrogen or C_{1-4} alkyl. Most preferably, R^{17} is $NR^{26}R^{27}$, wherein R^{26} and R^{27} are methyl.

[0031] Useful compounds also include those of Formula III wherein n is equal to a number from zero to four. Preferably, n is equal to a number from zero to two. More preferably, n is equal to zero.

[0032] A further aspect of the present invention is directed to compounds of Formula IV:



or a pharmaceutically acceptable salt thereof, wherein

n is equal to a number between zero and four,

R²⁹, R³⁰, R³¹, R³², R³³, R³⁴ and R³⁵ are independently selected from the group consisting of:

- a. hydrogen,
- b. C₁₋₄ alkylthio,
- c. C₁₋₄ alkylsulfonyl,
- d. hydroxy,
- e. C₁₋₄ alkoxy,
- f. NR⁶R⁷, wherein

R⁶ and R⁷ are hydrogen or C₁₋₄ alkyl,

- g. phenyl(C₁₋₄)alkyl,
- h. C₆₋₁₀ aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C₁₋₄)alkyl, and
- l. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

provided that one of R²⁹ through R³⁵ is monoalkylaminophenyl or dialkylaminophenyl; and

R^P is hydrogen or a sulfur protecting group, such as methoxymethyl, methoxyethoxymethyl, *p*-methoxybenzyl or benzyl.

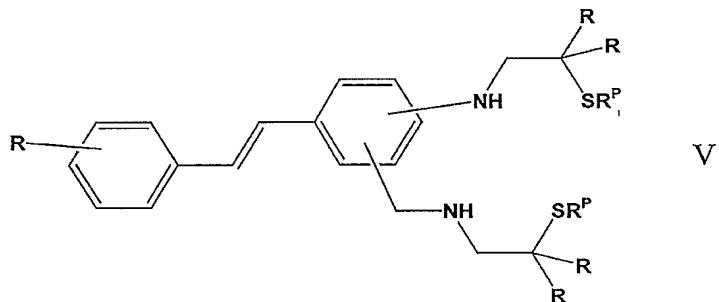
[0033] Useful compounds of Formula IV are those compounds wherein R²⁹, R³⁰, R³¹, R³², R³³, R³⁴ and R³⁵ are as described above. Preferable values of R²⁹ through R³⁵ falling under the scope of C₆₋₁₀ aryl include phenyl, naphthyl or tetrahydronaphthyl. Preferable values of R²⁹ through R³⁵ falling under the scope of heteroaryl include thienyl, furyl, pyranyl, pyrrolyl, pyridinyl, indolyl and imidazolyl. Preferable values of R²⁹ through R³⁵ falling under the scope of heterocycle include piperidinyl, pyrrolidinyl, and morpholinyl. In compounds wherein R²⁹ through R³⁵ are a preferred embodiment of a C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl, it is most preferable that the ring is substituted with one of the following: C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino. In another embodiment, especially useful compounds are those wherein R²⁹, R³⁰, R³¹, and R³³ are hydrogen. Within this embodiment, it is especially preferred that one of R³² and R³⁴ is as described above, the other of R³² and R³⁴ is hydrogen. More preferably, one of R³² and R³⁴ is aminophenyl, monoalkylaminophenyl or dialkylaminophenyl, the other of R³² and R³⁴ is hydrogen. Most preferably, one of R³² and R³⁴ is dimethylaminophenyl, the other of R³² and R³⁴ is hydrogen. Useful values of R³⁵ also include hydrogen, methoxy, C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, hydroxy and C₁₋₄ alkyl. Most preferably, R³⁵ is hydrogen or C₁₋₄ alkyl.

[0034] Useful compounds of Formula IV also include compounds wherein n is equal to a number from zero to four. More preferably, n is equal to zero or one. Most preferably, n is equal to zero.

[0035] It is also to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series.

[0036] The compounds of Formula I, II, III or IV may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds. In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0037] A further aspect of this invention is directed to compounds of Formula V:



or a pharmaceutically acceptable salt thereof or a derivative of compound of Formula V containing a radioisotope complex, wherein:

R is C₁₋₄ alkyl or is as defined for R²⁹-R³⁵ above, and

R^P is as defined above.

[0038] When any variable occurs more than one time in any constituent or in Formula I, II, III, IV or V its definition on each occurrence is independent of its definition at every other occurrence. Also combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0039] The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to 8 carbons, preferably 6 carbons, more preferably 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, and isobutyl.

[0040] The term "alkoxy" is used herein to mean a straight or branched chain alkyl radical, as defined above, unless the chain length is limited thereto,

bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, and the like. Preferably the alkoxy chain is 1 to 6 carbon atoms in length, more preferably 1-4 carbon atoms in length.

- [0041] The term "monoalkylamine" as employed herein by itself or as part of another group refers to an amino group which is substituted with one alkyl group as defined above.
- [0042] The term "dialkylamine" as employed herein by itself or as part of another group refers to an amino group which is substituted with two alkyl groups as defined above.
- [0043] The term "halo" employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine.
- [0044] The term "haloalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more chlorine, bromine, fluorine or iodine with fluorine and chlorine being preferred, such as chloromethyl, iodomethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and 2-chloroethyl.
- [0045] The term "alkylthio" as employed herein by itself or as part of another group refers to a thioether of the structure: R-S, wherein R is a C₁₋₄ alkyl as defined above.
- [0046] The term "alkylsulfonyl" as employed herein by itself or as part of another group refers to a sulfone of the structure: R-SO₂, wherein R is a C₁₋₄ alkyl as defined above.
- [0047] The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.
- [0048] The term "heterocycle" or "heterocyclic ring", as used herein except where noted, represents a stable 5- to 7- membered mono-heterocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O, and S, and wherein the nitrogen and sulfur heteroatom may optionally be oxidized. Especially useful are rings contain one nitrogen combined with one oxygen or sulfur, or two nitrogen heteroatoms. Examples of such heterocyclic groups include piperidinyl, pyrrolyl, pyrrolidinyl, imidazolyl,

imidazinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolidinyl, isothiazolyl, homopiperidinyl, homopiperazinyl, pyridazinyl, pyrazolyl, and pyrazolidinyl, most preferably thiamorpholinyl, piperazinyl, and morpholinyl.

[0049] The term "heteroatom" is used herein to mean an oxygen atom ("O"), a sulfur atom ("S") or a nitrogen atom ("N"). It will be recognized that when the heteroatom is nitrogen, it may form an NR^aR^b moiety, wherein R^a and R^b are, independently from one another, hydrogen or C₁₋₄ alkyl, C₂₋₄ aminoalkyl, C₁₋₄ halo alkyl, halo benzyl, or R¹ and R² are taken together to form a 5- to 7-member heterocyclic ring optionally having O, S or NR^c in said ring, where R^c is hydrogen or C₁₋₄ alkyl.

[0050] The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxythiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxyazinyl groups).

[0051] The term "aralkyl" or "arylalkyl" as employed herein by itself or as part of another group refers to C₁₋₆alkyl groups as discussed above having an aryl substituent, such as benzyl, phenylethyl or 2-naphthylmethyl.

[0052] Another aspect of this invention is related to methods of preparing compounds of Formula I, II, III, IV or V.

[0053] In embodiments of Formulae III, IV or V, the groups R^P are both hydrogen, or can be any of the variety of protecting groups available for sulfur, including methoxymethyl, methoxyethoxymethyl, *p*-methoxybenzyl or benzyl. Sulfur protecting groups are described in detail in Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd Edition, John

Wiley and Sons, Inc., New York (1991). Protecting group R^P can be removed by appropriate methods well known in the art of organic synthesis, such as trifluoroacetic acid, mercuric chloride or sodium in liquid ammonia. In the case of Lewis acid labile groups, including acetamidomethyl and benzamidomethyl, R^P can be left intact. Labeling of the ligand with technetium in this case will cleave the protecting group, rendering the protected diaminedithiol equivalent to the unprotected form.

[0054] Tc-99m complexes can be prepared as follows. A small amount of non-radiolabeled compound (1-2 mg) is dissolved in 100 μ L EtOH and mixed with 200 μ L HCl (1 N) and 1 mL Sn-glucoheptonate solution (containing 8-32 μ g SnCl₂ and 80-320 μ g Na-glucoheptonate, pH 6.67) and 50 μ L EDTA solution (0.1 N). [^{99m}Tc]Pertechnetate (100-200 μ L; ranging from 2-20 mCi) saline solution are then added. The reaction is heated for 30 min at 100° C, then cooled to room temperature. The reaction mixture is analyzed on TLC (EtOH:conc. NH₃ 9:1) for product formation and purity check. The mixture can be neutralized with phosphate buffer to pH 5.0.

[0055] The present invention further relates to a method of preparing a technetium-99m complex according to the present invention by reacting technetium-99m in the form of a pertechnetate in the presence of a reducing agent and optionally a suitable chelator with an appropriate Ch-containing compound.

[0056] The reducing agent serves to reduce the Tc-99m pertechnetate which is eluted from a molybdenum-technetium generator in a physiological saline solution. Suitable reducing agents are, for example, dithionite, formamidine sulphonic acid, diaminoethane disulphinate or suitable metallic reducing agents such as Sn(II), Fe(II), Cu(I), Ti(III) or Sb(III). Sn(II) has proven to be particularly suitable.

[0057] For the above-mentioned complex-forming reaction, technetium-99m is reacted with an appropriate compound of the invention as a salt or in the form of technetium bound to comparatively weak chelators. In the latter case the desired technetium-99m complex is formed by ligand exchange. Examples of suitable chelators for the radionuclide are dicarboxylic acids, such as oxalic acid, malonic acid, succinic acid, maleic acid, orthophthalic acid,

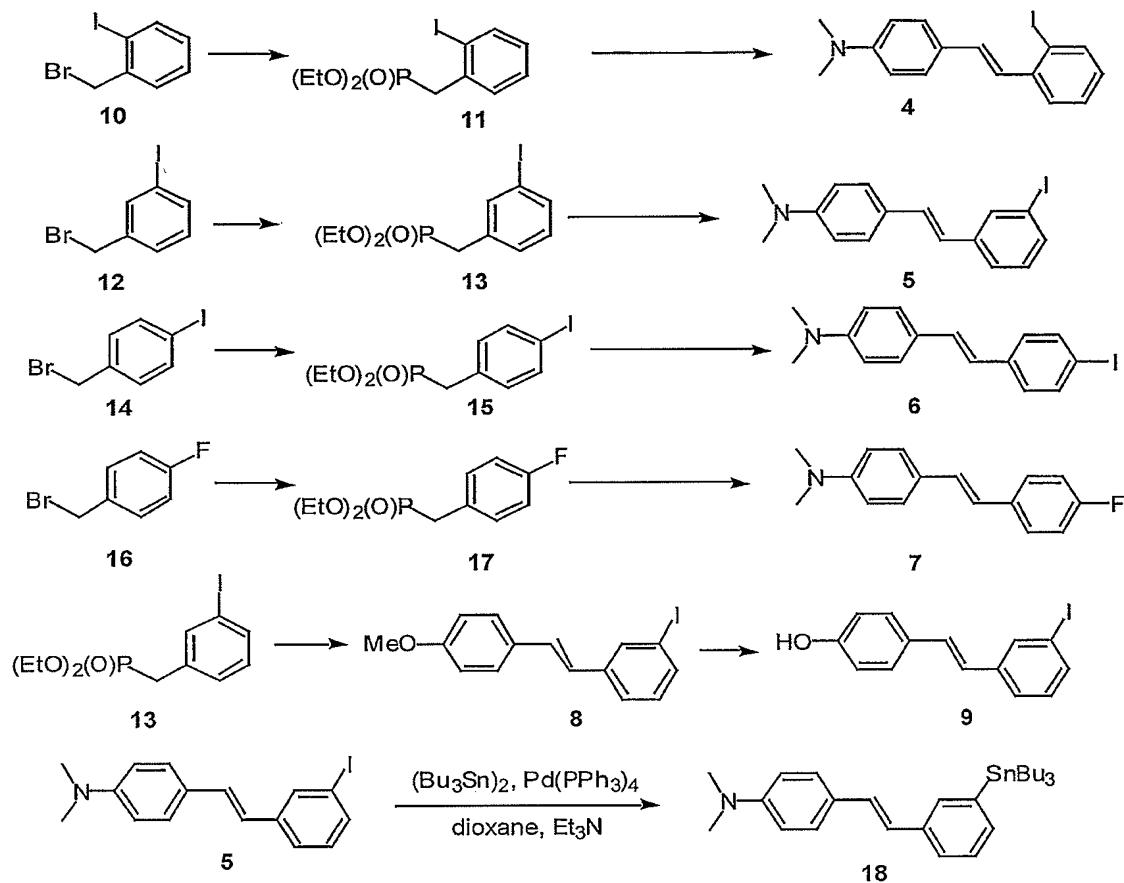
malic acid, lactic acid, tartaric acid, citric acid, ascorbic acid, salicylic acid or derivatives of these acids; phosphorus compounds such as pyrophosphates; or enolates. Citric acid, tartaric acid, ascorbic acid, glucoheptonic acid or a derivative thereof are particularly suitable chelators for this purpose, because a chelate of technetium-99m with one of these chelators undergoes the desired ligand exchange particularly easily.

[0058] The most commonly used procedure for preparing $[Tc^{99m}O]^{+3}N_2S_2$ complexes is based on stannous (II) chloride reduction of $[^{99m}Tc]pertechnetate$, the common starting material. The labeling procedure normally relies on a Tc-99m ligand exchange reaction between Tc-99m (Sn)-glucoheptonate and the N_2S_2 ligand. Preparation of stannous (II) chloride and preserving it in a consistent stannous (II) form is critically important for the success of the labeling reaction. To stabilize the air-sensitive stannous ion it is a common practice in nuclear medicine to use a lyophilized kit, in which the stannous ion is in a lyophilized powder form mixed with an excess amount of glucoheptonate under an inert gas like nitrogen or argon. The preparation of the lyophilized stannous chloride/sodium glucoheptonate kits ensures that the labeling reaction is reproducible and predictable. The N_2S_2 ligands are usually air-sensitive (thiols are easily oxidized by air) and there are subsequent reactions which lead to decomposition of the ligands. The most convenient and predictable method to preserve the ligands is to produce lyophilized kits containing 100-500 μg of the ligands under argon or nitrogen.

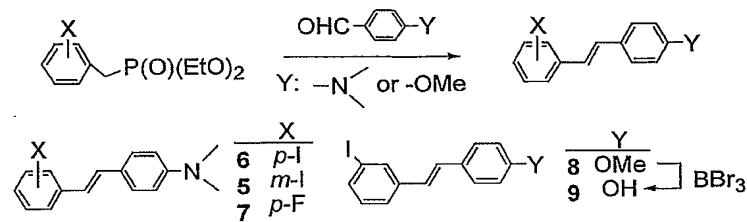
[0059] The present invention is further directed to methods of preparing compounds of the above Formula I, II, III, IV or V. The compounds of this invention can be prepared by reactions described in Schemes 1-9.

[0060] Schemes 1-5 depict a synthetic route for forming stilbene derivatives of Formula I using a Wittig reagent.

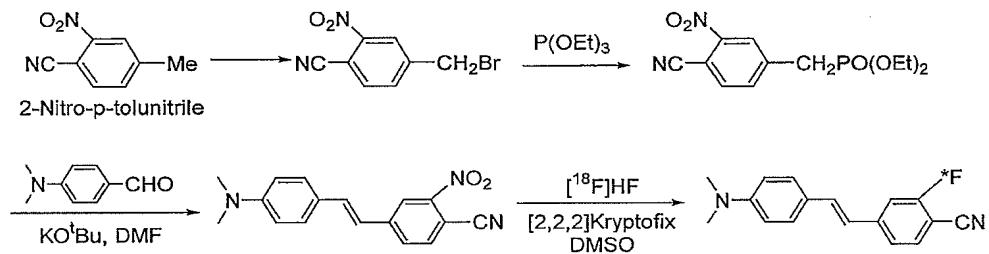
SCHEME 1



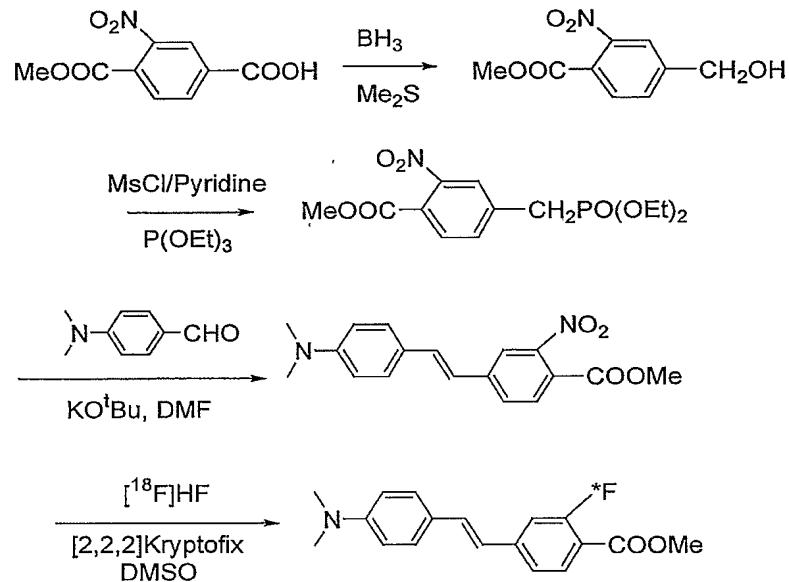
SCHEME 2



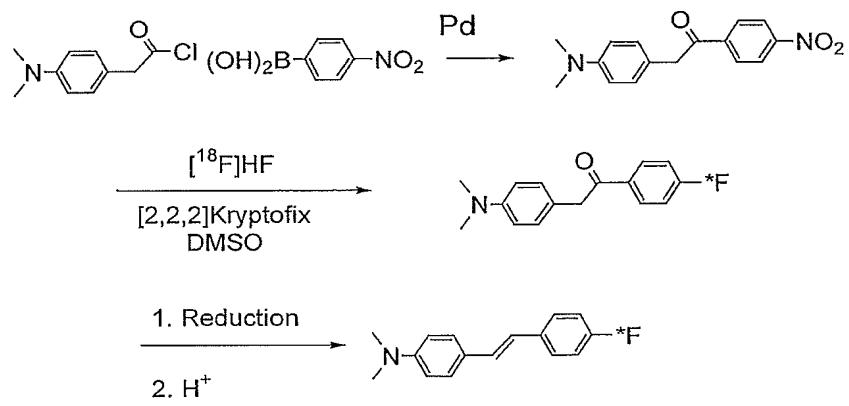
SCHEME 3



SCHEME 4



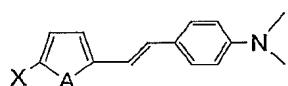
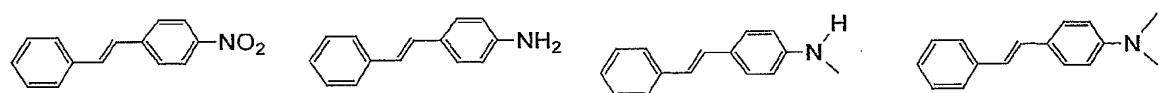
SCHEME 5



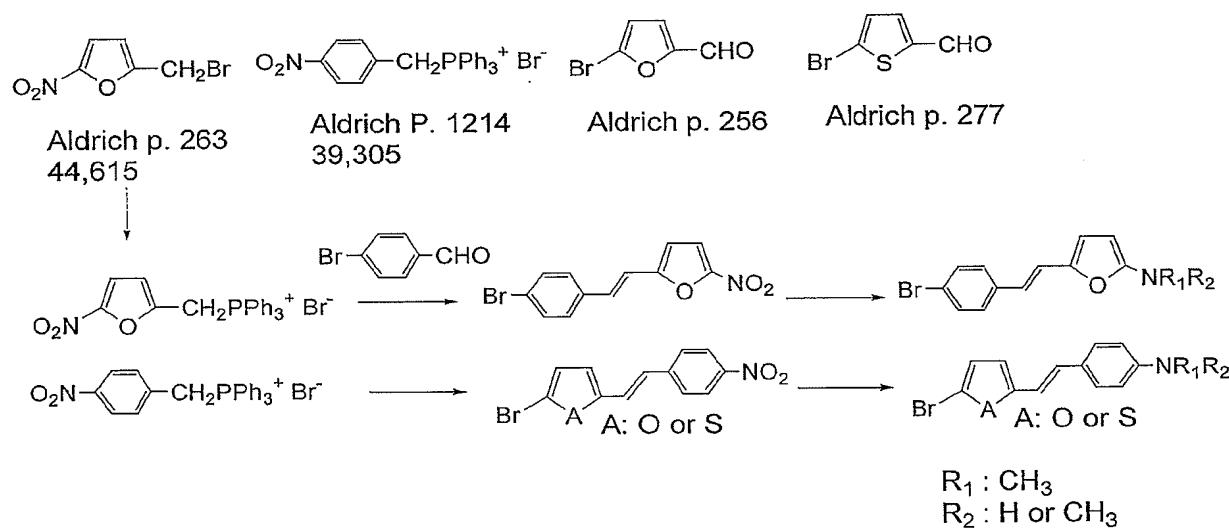
- 22 -

Scheme 6 depicts a synthetic route for forming derivatives of Formula II.

SCHEME 6



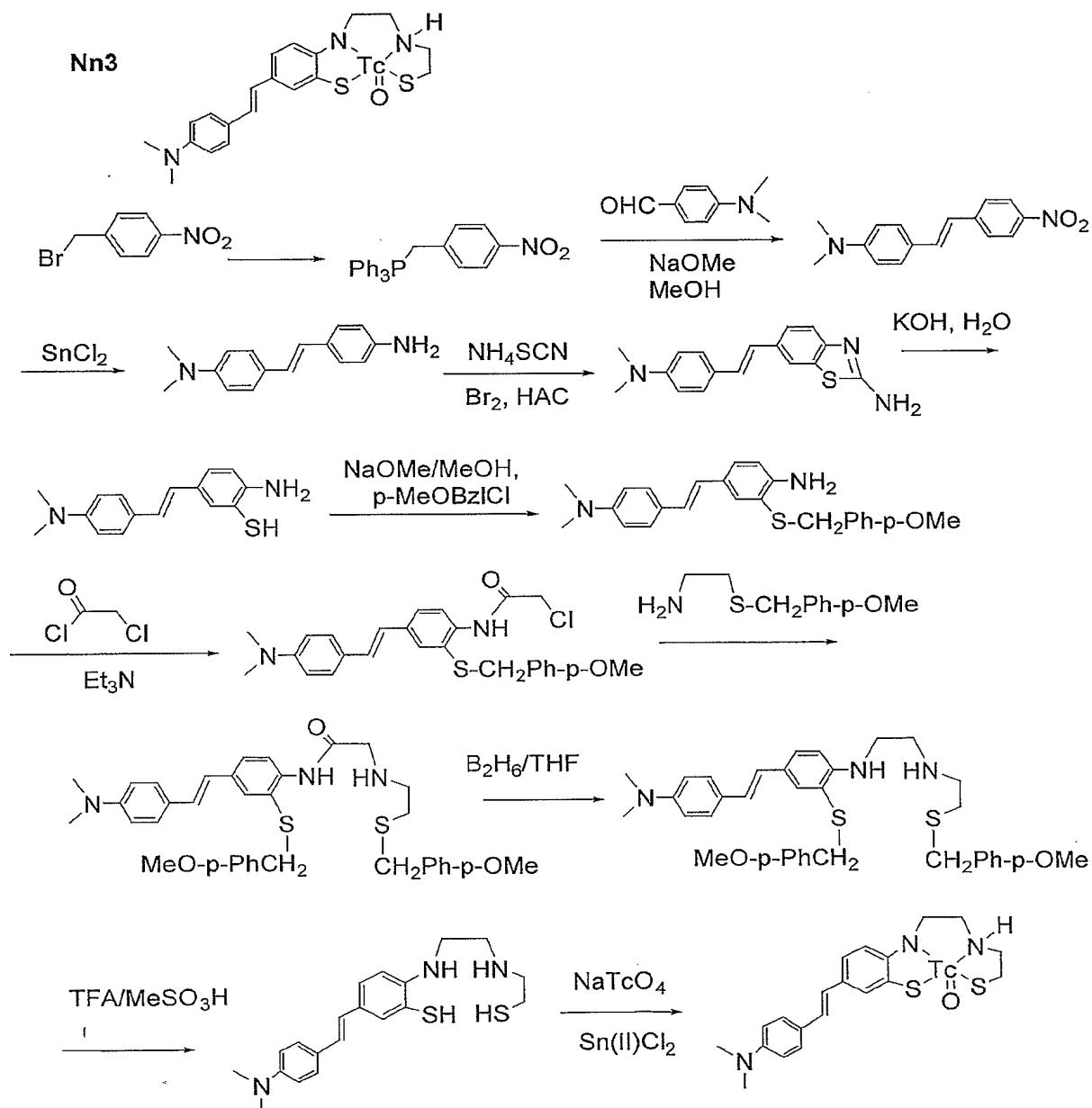
A: O or S
X: Br or I



- 23 -

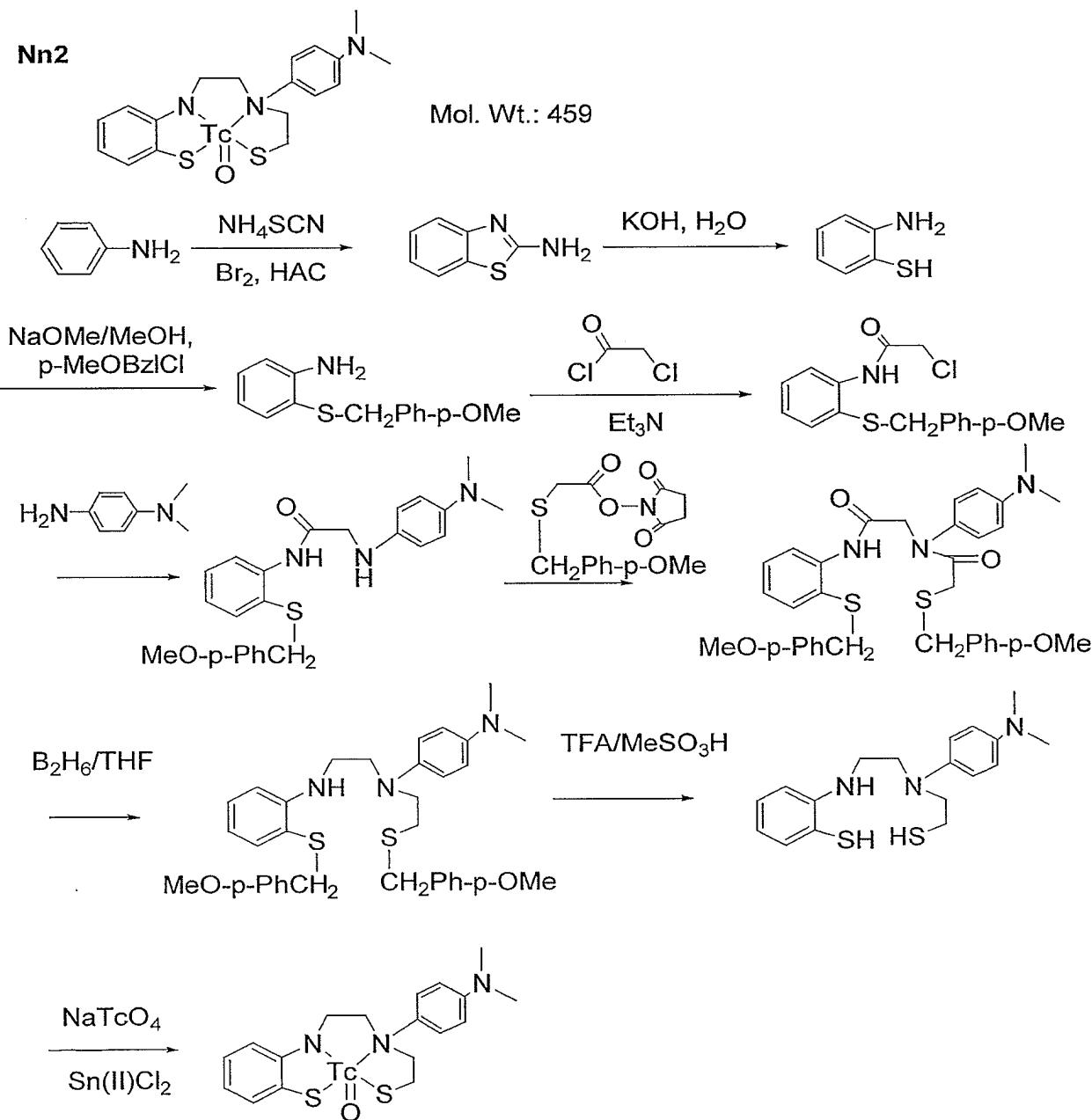
Scheme 7 depicts a synthetic route for forming derivatives of Formula III.

SCHEME 7



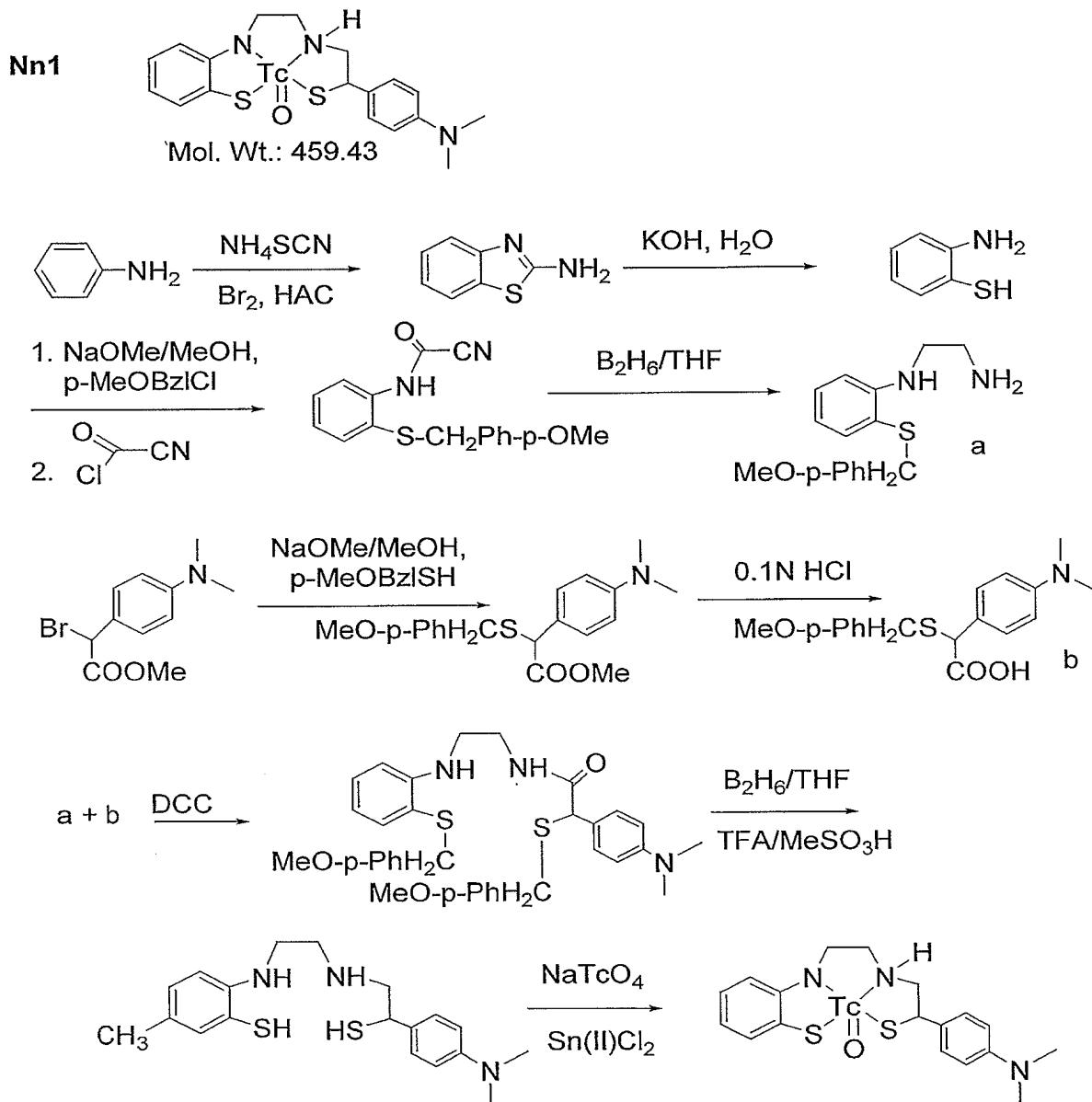
Scheme 8 depicts a synthetic route for derivatives of Formula IV.

SCHEME 8



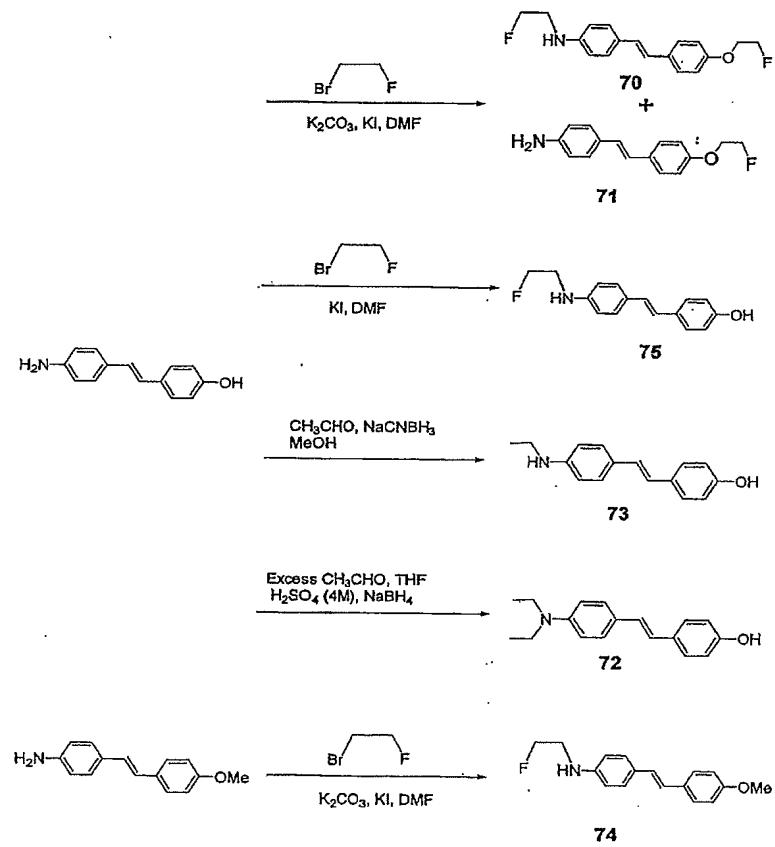
Scheme 9 depicts a synthetic route for forming derivatives of Formula IV.

SCHEME 9

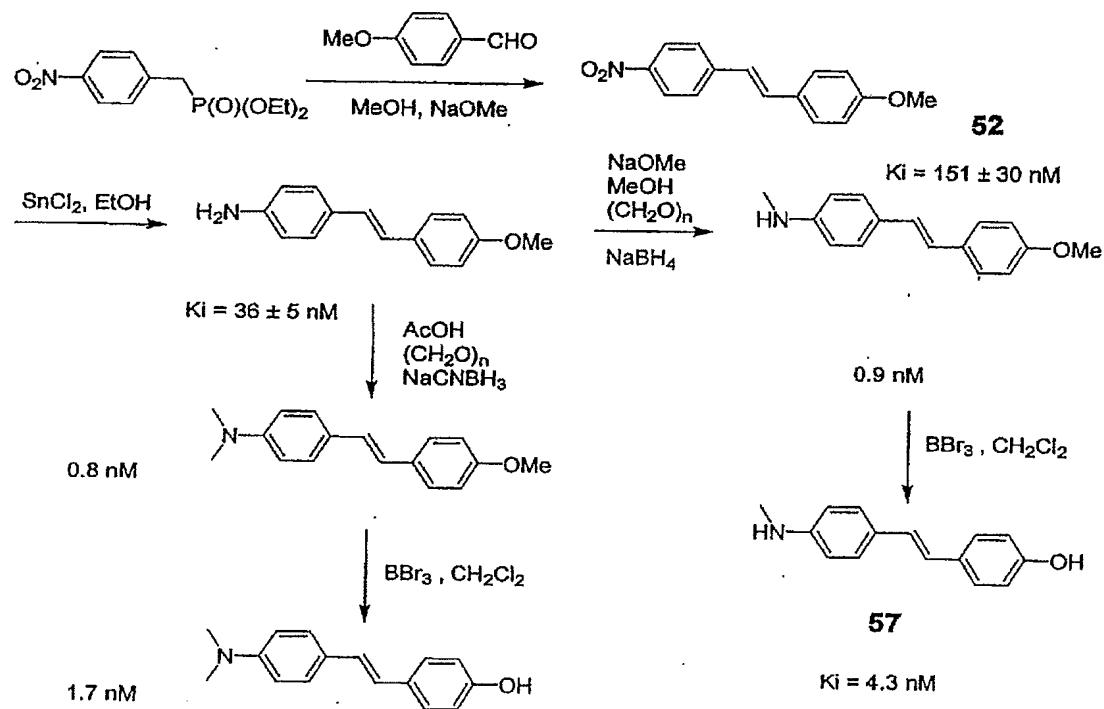


Schemes 10 and 11 depict synthetic routes for forming derivatives of Formula I.

SCHEME 10

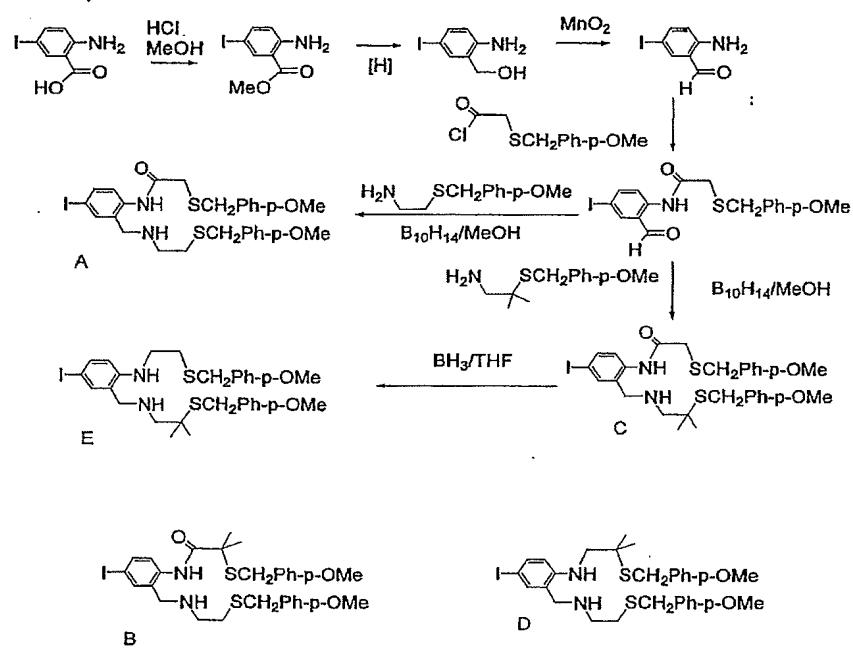


SCHEME 11



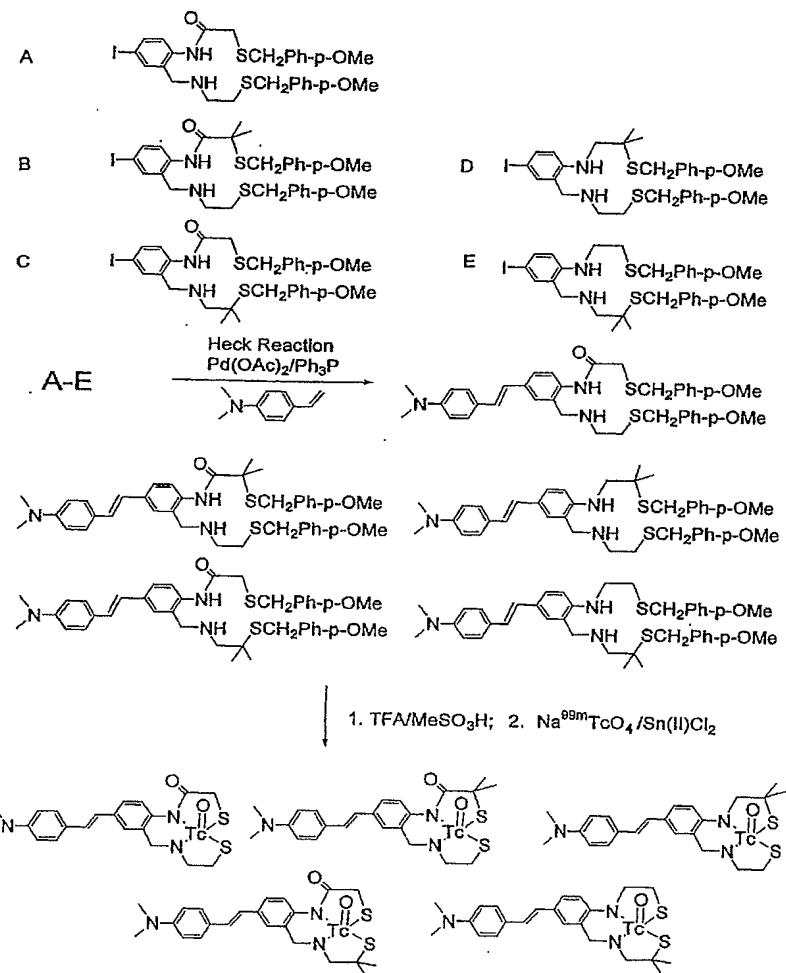
Scheme 12 depicts a synthetic route for forming intermediates of Formula V.

SCHEME 12



Scheme 13 depicts a synthetic route for forming derivatives of Formula V.

SCHEME 13



[0061] When the compounds of this invention are to be used as imaging agents, they must be labeled with suitable radioactive halogen isotopes. Although ^{125}I -isotopes are useful for laboratory testing, they will generally not be useful for actual diagnostic purposes because of the relatively long half-life (60 days) and low gamma-emission (30-65 Kev) of ^{125}I . The isotope ^{123}I has a half life of thirteen hours and gamma energy of 159 KeV, and it is therefore expected that labeling of ligands to be used for diagnostic purposes would be with this isotope. Other isotopes which may be used include ^{131}I (half life of 2 hours). Suitable bromine isotopes include ^{77}Br and ^{76}Br .

[0062] The radiohalogenated compounds of this invention lend themselves easily to formation from materials which could be provided to users in kits. Kits for forming the imaging agents can contain, for example, a vial containing a physiologically suitable solution of an intermediate of Formula I, II, III, IV or V in a concentration and at a pH suitable for optimal complexing conditions. The user would add to the vial an appropriate quantity of the radioisotope, e.g., Na^{123}I , and an oxidant, such as hydrogen peroxide. The resulting labeled ligand may then be administered intravenously to a patient, and receptors in the brain imaged by means of measuring the gamma ray or photo emissions therefrom.

[0063] Since the radiopharmaceutical composition according to the present invention can be prepared easily and simply, the preparation can be carried out readily by the user. Therefore, the present invention also relates to a kit, comprising:

(1) A non-radiolabeled compound of the invention, the compound optionally being in a dry condition; and also optionally having an inert, pharmaceutically acceptable carrier and/or auxiliary substances added thereto; and

(2) a reducing agent and optionally a chelator;

wherein ingredients (1) and (2) may optionally be combined; and further wherein instructions for use with a prescription for carrying out the above-described method by reacting ingredients (1) and (2) with technetium-99m in the form of a pertechnetate solution may be optionally included.

[0064] Examples of suitable reducing agents and chelators for the above kit have been listed above. The pertechnetate solution can be obtained by the user from a molybdenum-technetium generator. Such generators are available in a number of institutions that perform radiodiagnostic procedures. As noted above the ingredients (1) and (2) may be combined, provided they are compatible. Such a monocomponent kit, in which the combined ingredients are preferably lyophilized, is excellently suitable to be reacted by the user with the pertechnetate solution in a simple manner.

[0065] When desired, the radioactive diagnostic agent may contain any additive such as pH controlling agents (e.g., acids, bases, buffers), stabilizers (e.g., ascorbic acid) or isotonizing agents (e.g., sodium chloride).

[0066] The term "pharmaceutically acceptable salt" as used herein refers to those carboxylate salts or acid addition salts of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. Also included are those salts derived from non-toxic organic acids such as aliphatic mono and dicarboxylic acids, for example acetic acid, phenyl-substituted alkanoic acids, hydroxy alkanoic and alkanedioic acids, aromatic acids, and aliphatic and aromatic sulfonic acids. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Further representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, propionate, pivalate, cyclamate, isethionate, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium,

magnesium, and the like, as well as, nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S. M., *et al.*, *Pharmaceutical Salts, J. Pharm. Sci.* 66:1-19 (1977) which is incorporated herein by reference.)

[0067] In the first step of the present method of imaging, a labeled compound of Formula I, II, III, IV or V is introduced into a tissue or a patient in a detectable quantity. The compound is typically part of a pharmaceutical composition and is administered to the tissue or the patient by methods well known to those skilled in the art.

[0068] For example, the compound can be administered either orally, rectally, parenterally (intravenous, by intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments or drops), or as a buccal or nasal spray.

[0069] In a preferred embodiment of the invention, the labeled compound is introduced into a patient in a detectable quantity and after sufficient time has passed for the compound to become associated with amyloid deposits, the labeled compound is detected noninvasively inside the patient. In another embodiment of the invention, a labeled compound of Formula I, II, III, IV or V is introduced into a patient, sufficient time is allowed for the compound to become associated with amyloid deposits, and then a sample of tissue from the patient is removed and the labeled compound in the tissue is detected apart from the patient. In a third embodiment of the invention, a tissue sample is removed from a patient and a labeled compound of Formula I, II, III, IV or V is introduced into the tissue sample. After a sufficient amount of time for the compound to become bound to amyloid deposits, the compound is detected.

[0070] The administration of the labeled compound to a patient can be by a general or local administration route. For example, the labeled compound may be administered to the patient such that it is delivered throughout the body. Alternatively, the labeled compound can be administered to a specific organ or tissue of interest. For example, it is desirable to locate and quantitate amyloid

deposits in the brain in order to diagnose or track the progress of Alzheimer's disease in a patient.

[0071] The term "tissue" means a part of a patient's body. Examples of tissues include the brain, heart, liver, blood vessels, and arteries. A detectable quantity is a quantity of labeled compound necessary to be detected by the detection method chosen. The amount of a labeled compound to be introduced into a patient in order to provide for detection can readily be determined by those skilled in the art. For example, increasing amounts of the labeled compound can be given to a patient until the compound is detected by the detection method of choice. A label is introduced into the compounds to provide for detection of the compounds.

[0072] The term "patient" means humans and other animals. Those skilled in the art are also familiar with determining the amount of time sufficient for a compound to become associated with amyloid deposits. The amount of time necessary can easily be determined by introducing a detectable amount of a labeled compound of Formula I, II, III, IV or V into a patient and then detecting the labeled compound at various times after administration.

[0073] The term "associated" means a chemical interaction between the labeled compound and the amyloid deposit. Examples of associations include covalent bonds, ionic bonds, hydrophilic-hydrophilic interactions, hydrophobic-hydrophobic interactions, and complexes.

[0074] Those skilled in the art are familiar with the various ways to detect labeled compounds. For example, magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT) can be used to detect radiolabeled compounds. The label that is introduced into the compound will depend on the detection method desired. For example, if PET is selected as a detection method, the compound must possess a positron-emitting atom, such as ^{11}C or ^{18}F .

[0075] The radioactive diagnostic agent should have sufficient radioactivity and radioactivity concentration which can assure reliable diagnosis. For instance, in case of the radioactive metal being technetium-99m, it may be included usually in an amount of 0.1 to 50 mCi in about 0.5 to 5.0 ml at the time of administration. The amount of a compound of Formula I, II, III, IV or

V may be such as sufficient to form a stable chelate compound with the radioactive metal.

[0076] The thus formed chelate compound as a radioactive diagnostic agent is sufficiently stable, and therefore it may be immediately administered as such or stored until its use. When desired, the radioactive diagnostic agent may contain any additive such as pH controlling agents (e.g., acids, bases, buffers), stabilizers (e.g., ascorbic acid) or isotonizing agents (e.g., sodium chloride).

[0077] The imaging of amyloid deposits can also be carried out quantitatively so that the amount of amyloid deposits can be determined.

[0078] Preferred compounds for imaging include a radioisotope such as ^{123}I , ^{125}I , ^{131}I , ^{18}F , ^{76}Br or ^{77}Br .

[0079] The present invention is also directed at a method of imaging amyloid deposits. One of the key prerequisites for an *in vivo* imaging agent of the brain is the ability to cross the intact blood-brain barrier after a bolus *iv* injection.

[0080] Another aspect of the invention is a method of inhibiting amyloid plaque aggregation. The present invention also provides a method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, by administering to a patient an amyloid inhibiting amount of a compound of the above Formula I, II, III, IV or V.

[0081] Those skilled in the art are readily able to determine an amyloid inhibiting amount by simply administering a compound of Formula I, II, III, IV or V to a patient in increasing amounts until the growth of amyloid deposits is decreased or stopped. The rate of growth can be assessed using imaging as described above or by taking a tissue sample from a patient and observing the amyloid deposits therein. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is sufficient. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of

optimum dosages for a particular patient is well known to those skilled in the art.

[0082] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

Diethyl 2-iodobenzylphosphonate (11)

[0083] A mixture of 2-iodobenzyl bromide **10** (5 g, 16.84 mmol) and triethyl phosphite (3.3 g, 20 mmol) was stirred at 160 °C. After 4h, the mixture was cooled to room temperature. The residue was subjected to flash chromatography (EtOAc: Hex, 1:4), and gave 2.3 g of **11** (39%). ¹H NMR (200 MHz, CDCl₃): δ 1.24 (t, *J* = 7.04 Hz, 6H), 3.40 (d, *J* = 22.00 Hz, 2H), 4.03 (m, 4H), 6.91 (m, 1H), 7.32 (m, 1H), 7.44 (m, 1H), 7.82 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 16.27 (*J* = 6.00 Hz), 38.31 (*J* = 137.50 Hz), 62.16 (*J* = 6.70 Hz), 101.16 (*J* = 9.45 Hz), 128.23 (*J* = 3.35 Hz), 128.45 (*J* = 3.55 Hz), 130.60 (*J* = 5.10 Hz), 135.36 (*J* = 8.80 Hz), 139.60 (*J* = 2.85 Hz).

EXAMPLE 2

(*E*)-2'-Iodo-*N,N*-dimethyl-4-stilbenamine (4)

[0084] To a mixture of NaH (2 mmol, 80% suspension in oil), and 3-iodobenzylphosphonate **2** (500 mg, 1.42 mmol) in 6 mL of THF at 80°C under nitrogen atmosphere, was added dropwise 4-(dimethylamine)benzaldehyde (210 mg, 1.41 mmol). After overnight at room temperature, NH₄Cl solution (saturated, 5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extract was dried over Na₂SO₄ and evaporated to give (*E*)-2'-iodo-*N,N*-dimethyl-4-stilbenamine **11**, which was purified by

flash chromatography (EtOAc: Hex, 1:9) to give **3** (330 mg, 67%). ¹H NMR (200 MHz, CDCl₃): δ 3.06 (s, 6H), 6.82 (m, 2H), 6.93-7.02 (m, 1H), 7.01 (d, *J* = 15.98 Hz, 1H), 7.25 (d, *J* = 15.99 Hz, 1H), 7.40 (m, 1H), 7.53-7.59 (m, 2H), 7.69 (dd, *J* = 7.88 Hz, *J* = 1.54 Hz, 1H), 7.95 (dd, *J* = 7.92 Hz, *J* = 1.20 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 40.26, 100.20, 112.22, 125.12, 125.61, 127.83, 127.87, 127.97, 128.2, 131.66, 139.42, 140.84, 150.23; HRMS: m/z Calcd for C₁₆H₁₆IN: 349.0328; Found: 349.0342.

[0085]

EXAMPLE 3

Diethyl 3-iodobenzylphosphonate (13)

[0086] A mixture of 3-iodobenzyl bromide **12** (5 g, 16.84 mmol) and triethyl phosphite (3.3 g, 20 mmol) was stirred at 160 °C. After 4h, the mixture was cooled to room temperature. The residue was subjected to flash chromatography (EtOAc: Hex, 1:4), and gave 5.4 g of **13** (91%). ¹H NMR (200 MHz, CDCl₃): δ 1.15 (t, *J* = 7.05 Hz, 6H), 2.97 (d, *J* = 21.65 Hz, 2H), 3.92 (m, 4H), 6.93 (t, *J* = 7.76 Hz, 1H), 7.17 (m, 1H), 7.52 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 16.25 (*J* = 5.95 Hz), 33.15 (*J* = 137.60 Hz), 62.19 (*J* = 6.70 Hz), 94.13 (*J* = 3.50 Hz), 128.89 (*J* = 6.35 Hz), 130.07 (*J* = 3.00 Hz), 133.95 (*J* = 9.10 Hz), 135.87 (*J* = 3.55 Hz), 138.51 (*J* = 6.65 Hz).

EXAMPLE 4

(E)-3'-Iodo-*N,N*-dimethyl-4-stilbenamine (5)

[0087] To a mixture of NaH (2 mmol, 80% suspension in oil), and 3-iodobenzylphosphonate **13** (370 mg, 1.05 mmol) in 5 mL of THF at 80°C under nitrogen atmosphere, was added dropwise 4-(dimethylamine)benzaldehyde (155 mg, 1.05 mmol). After overnight at room temperature, NH₄Cl solution (saturated, 5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extract was dried over Na₂SO₄ and evaporated to give (E)-3'-iodo-*N,N*-dimethyl-4-stilbenamine **5**, which was purified by flash chromatography (EtOAc: Hex, 1:9) to give **3**

(209 mg, 57%). ^1H NMR (200 MHz, CDCl_3): δ 2.99 (s, 6H), 6.71 (m, 2H), 6.77 (d, J = 16.41 Hz, 1H), 7.02 (d, J = 16.22 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 7.36-7.52 (m, 4H), 7.82 (s, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 40.37, 49.78, 112.38, 112.53, 122.21, 127.76, 128.56, 130.19, 134.76, 135.34, 140.56, 150.36; HRMS: m/z Calcd for $\text{C}_{16}\text{H}_{16}\text{IN}$: 349.0328; Found: 349.0302.

[0088]

EXAMPLE 5

Diethyl 4-iodobenzylphosphonate (15)

[0089] A mixture of 4-iodobenzyl bromide **14** (5.2 g, 17.51 mmol) and triethyl phosphite (3.3 g, 20 mmol) was stirred at 160 °C. After 4h, the mixture was cooled to room temperature. The residue was subjected to flash chromatography (EtOAc: Hex, 1:4), and gave 3.27 g of **15** (53%). ^1H NMR (200 MHz, CDCl_3): δ 1.24 (t, J = 7.04 Hz, 6H), 3.07 (d, J = 21.72 Hz, 2H), 4.01 (m, 4H), 7.04 (m, 2H), 7.62 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 16.24 (J = 5.90 Hz), 33.21 (J = 137.55 Hz), 62.04 (J = 6.70 Hz), 92.15 (J = 4.80 Hz), 131.31 (J = 9.10 Hz), 131.57 (J = 6.55 Hz), 137.43 (J = 2.95 Hz).

EXAMPLE 6

(E)-4'-Iodo-*N,N*-dimethyl-4-stilbenamine (6)

[0090] To a mixture of NaH (2 mmol, 80% suspension in oil), and 4-iodobenzylphosphonate **15** (420 mg, 1.19 mmol) in 5 mL of THF at 80°C under nitrogen atmosphere, was added dropwise 4-(dimethylamine)benzaldehyde (180 mg, 1.20 mmol). After overnight at room temperature, water (5 mL) was added. The solid formed was filtered and washed with ether to give crude **6** which was purified by recrystallization with CH_2Cl_2 /hexane to afford pure **6** (156 mg, 38%). ^1H NMR (200 MHz, CDCl_3): δ 2.99 (s, 6H), 6.71 (d, J = 8.60 Hz, 2H), 6.81 (d, J = 16.65 Hz, 1H), 7.04 (d, J = 16.12 Hz, 1H), 7.21 (d, J = 8.15 Hz, 1H), 7.38 (d, J = 8.59 Hz, 2H), 7.63 (d, J = 8.28 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 40.39, 91.32, 112.38, 123.04,

127.69, 127.73, 128.23, 129.65, 137.55, 137.77, 150.29; HRMS: m/z Calcd for C₁₆H₁₆IN: 349.0328; Found: 349.0288.

EXAMPLE 7

(E)-4'-Iodo-4-O-methoxystilbenol (8)

[0091] To a mixture of NaH (2 mmol, 80% suspension in oil), and 3-iodobenzylphosphonate **13** (450 mg, 1.27 mmol) in 7 mL of THF at 80°C under nitrogen atmosphere, was added dropwise *p*-anisaldehyde (172 mg, 1.27 mmol). After 3 days at room temperature, NH₄Cl solution (saturated, 5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extract was dried over Na₂SO₄, evaporated and purified by flash chromatography (EtOAc: Hex, 1:9) to give (E)-1-iodo-3-[2-(4-methoxyphenyl)ethenyl] benzene **8** (400 mg, 90%). ¹H NMR (200 MHz, CDCl₃): δ 3.84 (s, 3H), 6.84 (d, *J* = 16.29 Hz, 1H), 6.90 (m, 2H), 7.05 (d, *J* = 16.30 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.42-7.56 (m, 4H), 7.85 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 55.32, 94.76, 114.20, 124.85, 125.48, 127.88, 129.58, 129.62, 130.25, 135.00, 135.91, 139.97, 159.62; HRMS: m/z Calcd for C₁₅H₁₃IO: 336.0011; Found: 336.0006.

EXAMPLE 8

(E)-3'-Iodo-4-stilbenol (9)

[0092] To a solution of **8** (350 mg, 1.00 mmol) in CH₂Cl₂ (200 mL) was added BBr₃ (10 mL, 1M in hexane) dropwise at -78°C in a dry ice-acetone bath. The mixture was allowed to warm up to room temperature. Water was added while the reaction mixture was cooled at 0°C in an ice bath. The mixture was extracted with CH₂Cl₂. The organic phase was dried and filtered. The filtrate was purified by flash chromatography (EtOAc: Hex, 1:9) to give **9** (296 mg, 92%). ¹H NMR (200 MHz, CDCl₃): δ 4.81 (s, 1H), 6.83 (d, *J* = 16.17 Hz, 1H), 6.84 (m, 2H), 7.03 (d, *J* = 16.32 Hz, 1H), 7.06 (t, *J* = 7.8 Hz,

1H), 7.36-7.57 (m, 4H), 7.84 (s, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 94.75, 115.67, 124.96, 125.49, 128.09, 129.48, 129.87, 130.25, 135.01, 135.96, 139.90, 155.53; HRMS: m/z Calcd for $\text{C}_{14}\text{H}_{11}\text{IO}$: 321.9855; Found: 321.9840.

EXAMPLE 9

Diethyl, 4-fluorobenzylphosphonate (17)

[0093] A mixture of 4-fluorobenzyl bromide **16** (1.89 g, 10 mmol) and triethyl phosphite (1.66 g, 10 mmol) was stirred at 170 °C for 4 h. The mixture was cooled to room temperature. and the residue was subjected to flash chromatography (EtOAc: Hex, 1:4) to gave 1.4 g of **17**(57%).
 ^1H NMR (200 MHz, CDCl_3): δ 1.23 (t, $J = 7.1$ Hz, 6H), 3.10 (d, $J = 21.4$ Hz, 2H), 3.92 (q, $J = 7.1$ Hz, 4H), 7.02 (m, 2H), 7.25 (m, 2H).

EXAMPLE 10

(E)-4-Fluoro-4'-dimethylamino-stilbene (7):

[0094] To a mixture of phosphate **17** (246 mg, 1 mmol) and 4-dimethylaminobenzaldehyde (149 mg, 1 mmol) in DMF (2 mL) was added KO^tBu (224 mg, 2 mmol) in portions in solid form at RT. The resulting mixture was stirred at RT overnight. Water (10 mL) was added The solid was collected by suction and washed with water, dried to give 190 mg of product (80%).

[0095] ^1H NMR (200 MHz, CDCl_3): δ 2.99 (s, 6H), 6.71 (d, $J = 8.9$ Hz, 2H), 6.85 (d, $J = 16.3$ Hz, 1H), 7.01 (t, $J = 8.7$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H), 7.43 (m, 2H); ^{13}C NMR (200 MHz, CDCl_3): δ 41.00, 113.01, 115.78, 116.21, 123.76, 126.18, 127.83, 127.99, 128.05, 129.19, 134.91, 150.72, 164.81.

EXAMPLE 11

(E)-3-Tributylstannyl-4'-dimethylamino-stilbene (18)

[0096] A mixture of **5** (139 mg, 0.38 mmol), bis-(tributyltin) (0.4 mL) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (30 mg) in a mixed solvent (20 mL, dioxane:triethylamine, 3:1) was stirred at 90 °C overnight. Solvent was removed and the residue was purified by PTLC (Hex:EtOAc, 2:1) to give 35 mg of product (18%, not optimized yield). ^1H NMR (200 MHz, CDCl_3): δ 0.94 (t, J = 7.2 Hz, 9H), 1.08-1.66 (m, 18H), 3.01 (s, 6H), 6.75 (m, 2H), 6.94 (d, J = 16.3 Hz, 1H), 7.08 (d, J = 16.3 Hz, 1H), 7.25-7.57 (m, 6H); ^{13}C NMR (50 MHz, CDCl_3): δ 9.56, 13.67, 27.37, 29.10, 40.45, 112.45, 124.84, 125.44, 125.98, 127.51, 128.01, 128.51, 134.36, 134.89, 137.41, 142.09, 150.06; HRMS: m/z Calcd for $\text{C}_{28}\text{H}_{44}\text{NSn} (\text{MH}^+)$: 514.2496; Found: 514.2512.

EXAMPLE 12

Preparation of radioiodinated ligand

[0097] The desired ^{125}I -labeled compound was prepared using iododestannylation reactions with tributyltin precursor of **5**. Hydrogen peroxide (50 μL , 3% w/v) was added to a mixture of 50 μL of the corresponding tributyltin precursor, **18**, (1 $\mu\text{g}/\mu\text{L}$ EtOH), 50 μL of 1N HCl and $[^{125}\text{I}]\text{NaI}$ (1-5 mCi) in a closed vial. The reaction was allowed to proceed for 10 min at room temperature and terminated by addition of 100 μL of sat. NaHSO_3 . The reaction mixture was extracted with ethyl acetate (3 x 1 mL) after neutralization with saturated sodium bicarbonate solution. The combined extracts were evaporated to dryness. The residue was dissolved in 100 μL of EtOH and purified by HPLC using a reversed phase column (Waters C-18 ubondpad, 3.9 x 300 mm) with an isocratic solvent of 80 % acetonitrile-20 % of buffer, 3,3-dimethylglutaric acid (5 mM, pH 7.0) in a flow rate of 0.8 mL/min. The desired fractions containing the product were collected, condensed and re-extracted with ethyl acetate. The no-carrier-added product

was evaporated to dryness and re-dissolved in 100% EtOH (1 μ Ci/ μ L). The final 125 I probe, with a specific activity of 2,200Ci/mmole and a greater than 95% radiochemical purity, was stored at -20 °C up to 6 weeks for *in vitro* binding studies.

EXAMPLE 13

Binding assays using aggregated A β (1-40) peptide in solution

[0098] The solid forms of peptides A β (1-40) was purchased from Bachem (King of Prussia, PA). Peptide aggregation was carried out by gently dissolving the peptide (0.5 mg/mL) in a buffer solution (pH 7.4) containing 10 mM sodium phosphate and 1mM EDTA. The solution was incubated at 37°C for 36-42 h with gentle and constant shaking. Binding studies were carried out in 12 x 75 mm borosilicate glass tubes according to the procedure described¹. Aggregated fibrils (10-50 nM in the final assay mixture) were added to the mixture containing 50 μ l of radioligands (0.01-0.5 nM in 40% EtOH) and 10 % EtOH in a final volume of 1 mL for saturation studies. The final concentration of EtOH was 10%. Nonspecific binding was defined in the presence of 2 μ M thioflavin T. For inhibition studies, 1mL of the reaction mixture contained 40 μ l of inhibitors (10^{-5} - 10^{-10} M in 10 % EtOH) and 0.05 nM radiotracer in 40 % EtOH. The mixture was incubated at room temperature for 3 h and the bound and the free radioactivities were separated by vacuum filtration through Whatman GF/B filters using a Brandel M-24R cell harvester followed by 2 x 3 mL washes of 10% ethanol at room temperature. Filters containing the bound I-125 ligand were counted in a gamma counter (Packard 5000) with 70% counting efficiency. Under the assay conditions, the percent of the specifically bound fraction was less than 20% of the total radioactivity. The results of saturation and inhibition experiments were subjected to nonlinear regression analysis using software EBDA² by which K_d and K_i values were calculated. Values for (K_i , nM) are the mean \pm SEM of three independent experiments, each in duplicate.

Additional K_i values for compounds of Formula I are provided in Figures 1 and 2.

[0099] In *in vitro* binding assays using pre-formed A β aggregates of synthetic peptides and [^{125}I]TZDM as the ligand, these novel stilbenes showed exceedingly high binding affinity (2-40 nM) to the TZ sites, while the affinity towards SB sites was very low (>1,000 nM). It is evident that the stilbenes containing an electron donating groups, such as dimethylamino-, -OH or -OMe group, showed excellent binding affinity to A β aggregates. Benzothiazole ring appears to be unnecessary for binding at the TZ binding sites of A β aggregates. This information is of paramount importance because it reduces the molecular size (molecular weight of TZDM and 1 was 380 and 349, respectively) required for binding to the TZ sites; as such it significantly enhances the flexibility on designing new ligands. The iodinated stilbenes, such as 2 and 5, represent a structural simplicity, which suggests minimum requirements for binding the A β aggregates may be three: 1) two benzene rings separated by a vinyl group. 2) one of the aromatic ring contains an electronic negative group, dimethylamino-, -OH or -OMe group. 3) there appears to be a bulk tolerance for substitution on the second aromatic ring. To characterize the compounds further, radioactive iodinated ligand, [^{125}I]2, was prepared by converting the corresponding tributyltin derivative in the presence of Na[^{125}I]I and hydrogen peroxide, by which the no-carrier added product was obtained in excellent yield (radiochemical purity > 95%). The direct binding assay showed that the new evaluation of postmortem AD brain sections with [^{125}I]2 suggested that the novel ligand, as expected, labeled A β plaques.

EXAMPLE 14

In vivo biodistribution of new probes in normal mice

[00100] While under ether anesthesia, 0.15 mL of a saline solution containing the labeled agent (5-10 μCi) was injected directly into the tail vein of ICR mice (2-3 month-old, average weight 20-30 g). The mice were sacrificed by

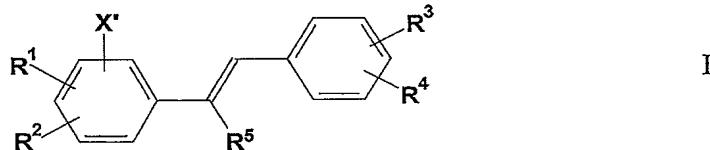
cardiac excision at various time points post injection. The organs of interest were removed and weighed, and the radioactivity was counted with an automatic gamma counter (Packard 5000). The percentage dose per organ was calculated by a comparison of the tissue counts to suitably diluted aliquots of the injected material. Total activities of blood and muscle were calculated under the assumption that they were 7% and 40% of the total body weight, respectively.

[00101] *In vivo* biodistribution study of [¹²⁵I]2 in normal mice after an iv injection suggested good brain penetration. The brain uptake was 0.84, 1.08, 0.91, and 0.54 %dose/organ, at 2, 30, 60 and 120 minutes after injection (the blood levels was relatively low 5.2-3.6 %dose/organ at all of the time points). Radioactive ligand's binding to the aggregates of A β ₁₋₄₀ is saturable and the K_d was 0.2 nM.

[00102] Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound of general Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^5 is hydrogen or C_{1-4} alkyl;

R^1 , R^2 and R^3 , in each instance, is independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, cyano, carboxy(C_{1-5})alkyl, trifluoromethyl, nitro, methylamino, dimethylamino, halo(C_{1-4})alkyl, and formyl;

R^4 is selected from the group consisting of:

- a. C_{1-4} alkylthio,
- b. halo(C_{1-4})alkoxy,
- c. carboxy(C_{1-5})alkyl,
- d. hydroxy,
- e. C_{1-4} alkoxy,
- f. NR^6R^7 , wherein

R^6 and R^7 are hydrogen, fluoro(C_{1-4})alkyl or C_{1-4} alkyl,

- g. phenyl(C_{1-4})alkyl,
- h. C_{6-10} aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C_{1-4})alkyl, and
- l. C_{3-6} cycloalkyl,

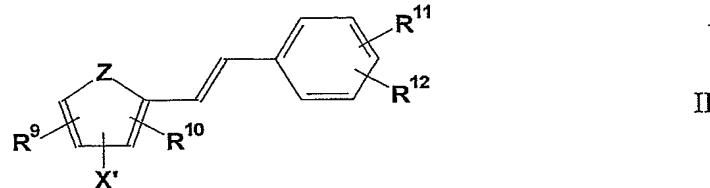
wherein said phenyl(C_{1-4})alkyl, C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl is substituted with one of the following: C_{1-4} alkylthio, C_{1-4} alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

and,

X' is ^{125}I , ^{123}I , ^{131}I , ^{18}F , $^{18}\text{Fluoro}(\text{C}_{1-4})\text{alkyl}$, $[^{18}\text{Fluoro}(\text{C}_{1-4})\text{alkyl}]$ amino, $[^{18}\text{Fluoro}(\text{C}_{1-4})\text{alkyl}]$ alkylamino, ^{76}Br , ^{77}Br or $\text{Sn}(\text{alkyl})_3$.

2. A compound of claim 1, wherein
 R^5 is hydrogen or methyl; and
 R^3 is hydrogen.
3. A compound of claim 1, wherein
 R^1 and R^2 are hydrogen or C_{1-4} alkyl.
4. A compound of claim 3, wherein
 R^5 is hydrogen.
5. A compound of claim 4, wherein
 R^1 is hydrogen, and
 R^4 is C_{1-4} alkylthio, halo(C_{1-4})alkoxy, hydroxy, C_{1-4} alkoxy or
 NR^6R^7 , wherein
 R^6 and R^7 are hydrogen, fluoro(C_{1-4})alkyl or C_{1-4} alkyl.
6. A compound of claim 5, wherein
 R^2 is hydrogen.
7. A compound of claim 1, wherein
 R^4 is methylthio, hydroxy, methoxy or NR^6R^7 ,
wherein R^6 and R^7 are hydrogen, fluoro(C_{1-4})alkyl or
methyl.
8. A compound of claim 1, wherein
 X' is ^{123}I .

9. A compound of general Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

Z is O, S or NR^a, wherein

R^a is C₁₋₄ alkyl;

R^9 , R^{10} and R^{11} , in each instance, is independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, cyano, carboxy(C_{1-5})alkyl, trifluoromethyl, nitro, methylamino, dimethylamino, halo(C_{1-4})alkyl, and formyl;

R^{12} is selected from the group consisting of:

- a. C₁₋₄ alkylthio,
- b. halo(C₁₋₄)alkoxy,
- c. carboxy(C₁₋₅)alkyl,
- d. hydroxy,
- e. C₁₋₄ alkoxy,
- f. NR¹³R¹⁴, wherein

R¹³ and R¹⁴ are hydrogen, fluoro(C₁₋₄)alkyl or C₁₋₄ alkyl,

- g. phenyl(C₁₋₄)alkyl,
- h. C₆₋₁₀ aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C₁₋₄)alkyl, and
- l. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

and,

X' is ^{125}I , ^{123}I , ^{131}I , ^{18}F , $^{18}\text{Fluoro(C}_{1-4}\text{)alkyl}$, $[^{18}\text{Fluoro(C}_{1-4}\text{)alkyl}]$ amino, $[^{18}\text{Fluoro(C}_{1-4}\text{)alkyl}]$ alkylamino, ^{76}Br , ^{77}Br or Sn(alkyl)_3 .

10. A compound of claim 9, wherein
 R^{11} is hydrogen.

11. A compound of claim 9, wherein
 R^9 and R^{10} are hydrogen or C_{1-4} alkyl.

12. A compound of claim 9, wherein
 Z is O.

13. A compound of claim 9, wherein
 R^9 is hydrogen,
 R^{12} is C_{1-4} alkylthio, halo(C_{1-4})alkoxy, hydroxy, C_{1-4} alkoxy or
 $\text{NR}^{13}\text{R}^{14}$, wherein
 R^{13} and R^{14} are hydrogen, fluoro(C_{1-4})alkyl or C_{1-4} alkyl.

14. A compound of claim 13, wherein
 R^{10} is hydrogen.

15. A compound of claim 9, wherein
 R^{12} is methylthio, hydroxy, methoxy, or $\text{NR}^{13}\text{R}^{14}$,

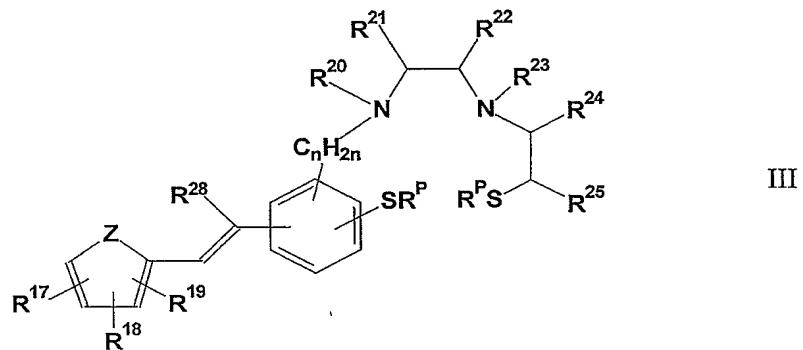
wherein R¹³ and R¹⁴ are hydrogen, fluoro(C₁₋₄)alkyl or

methyl.

16. A compound of claim 15, wherein

X' is ¹²³I.

17. A compound of general Formula III:



or a pharmaceutically acceptable salt thereof, wherein:

R²⁸ is hydrogen or C₁₋₄ alkyl,

n is equal to a number from zero to four,

Z is O, S or -CR¹⁵=CR¹⁶-, wherein

R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ are independently selected from the group consisting of:

- a. hydrogen
- b. C₁₋₄ alkylthio,
- c. hydroxy,
- d. C₁₋₄ alkoxy,
- e. NR²⁶R²⁷, wherein

R²⁶ and R²⁷ are hydrogen or C₁₋₄ alkyl,

- f. phenyl(C₁₋₄)alkyl,
- g. C₆₋₁₀ aryl,
- h. heteroaryl,
- i. heterocycle,
- j. heterocycle(C₁₋₄)alkyl, and

k. C_{3-6} cycloalkyl,

wherein said phenyl(C_{1-4})alkyl, C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl is substituted with one of the following: C_{1-4} alkylthio, C_{1-4} alkyl, methoxy, hydroxy, dimethylamino or methylamino;

provided that one or more of R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} and R^{25} is other than hydrogen;
and,

R^P is hydrogen or a sulfur protecting group, such as methoxymethyl, methoxyethoxymethyl, *p*-methoxybenzyl or benzyl.

18. A compound of claim 17, wherein Z is O.

19. A compound of claim 17, wherein Z is S.

20. A compound of claim 17, wherein Z is
 $CR^{15}=CR^{16}$, wherein
 R^{15} and R^{16} , in each instance, is as described above.

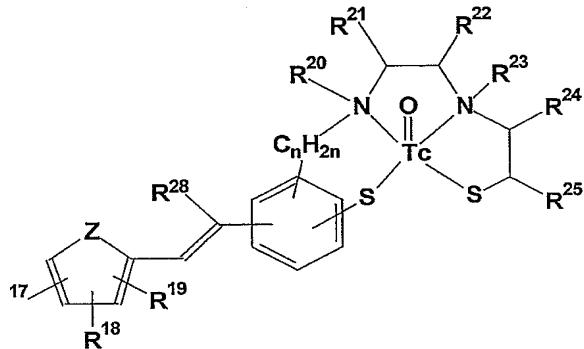
21. A compound of claim 17, wherein
 R^{17} is $NR^{26}R^{27}$, wherein
 R^{26} and R^{27} are as described above, and
 R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{28} are hydrogen.

22. A compound of claim 20, wherein n is equal to zero.

23. A compound of claim 17, wherein R^{26} and R^{27} are independently hydrogen or C_{1-4} alkyl.

24. A compound of claim 23, wherein R^{26} and R^{27} are methyl.

25. A compound containing a radioisotope complex and having the Formula:



wherein:

R²⁸ is hydrogen or C₁₋₄ alkyl,

n is equal to a number from zero to four,

Z is O, S or -CR¹⁵=CR¹⁶-, wherein

R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ are independently selected from the group consisting of:

- a. hydrogen
- b. C₁₋₄ alkylthio,
- c. hydroxy,
- d. C₁₋₄ alkoxy,
- e. NR²⁶R²⁷, wherein

R²⁶ and R²⁷ are hydrogen or C₁₋₄ alkyl,

- f. phenyl(C₁₋₄)alkyl,
- g. C₆₋₁₀ aryl,
- h. heteroaryl,
- i. heterocycle,
- j. heterocycle(C₁₋₄)alkyl, and
- k. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄

alkylthio, C₁₋₄ alkyl, methoxy, hydroxy, dimethylamino or methylamino;

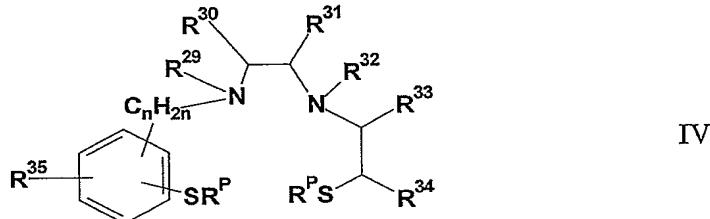
with the provisos that,

- a) one or more of R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²⁴ and R²⁵ is other than hydrogen; and
- b) one of R²⁰ and R²³ is selected from the group consisting of:
 - a. hydrogen,
 - b. phenyl(C₁₋₄)alkyl,
 - c. C₆₋₁₀ aryl,
 - d. heteroaryl,
 - e. heterocycle,
 - f. heterocycle(C₁₋₄)alkyl, and
 - g. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

the other of R²⁰ and R²³ represents an unsubstituted position.

26. A compound of general Formula IV:



or a pharmaceutically acceptable salt thereof, wherein:

n is equal to a number between zero and four,

R²⁹, R³⁰, R³¹, R³², R³³, R³⁴ and R³⁵ are independently selected

from the group consisting of:

- a. hydrogen,
- b. C₁₋₄ alkylthio,
- c. C₁₋₄ alkylsulfonyl,
- d. hydroxy,
- e. C₁₋₄ alkoxy,
- f. NR⁶R⁷, wherein

R⁶ and R⁷ are hydrogen or C₁₋₄ alkyl,

- g. phenyl(C₁₋₄)alkyl,
- h. C₆₋₁₀ aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C₁₋₄)alkyl, and
- l. C₃₋₆ cycloalkyl,

wherein said phenyl(C₁₋₄)alkyl, C₆₋₁₀ aryl, heteroaryl, heterocycle, heterocycle(C₁₋₄)alkyl or C₃₋₆ cycloalkyl is substituted with one of the following: C₁₋₄ alkylthio, C₁₋₄ alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino;

provided that one of R²⁹ through R³⁵ is monoalkylaminophenyl or dialkylaminophenyl; and

R^P is hydrogen or a sulfur protecting group, such as methoxymethyl, methoxyethoxymethyl, p-methoxybenzyl or benzyl.

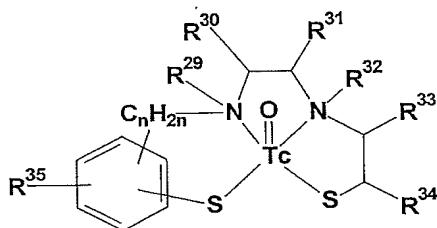
27. A compound of claim 26, wherein
 R^{34} is monoalkylaminophenyl or dialkylaminophenyl.

28. A compound of claim 26, wherein
 R^{34} is monomethylaminophenyl or dimethylaminophenyl,
 R^{29} , R^{30} , R^{31} , R^{32} , R^{33} and R^{35} are hydrogen, and
 n is equal to zero.

29. A compound of claim 26, wherein
 R^{32} is monoalkylaminophenyl or dialkylaminophenyl.

30. A compound of claim 29, wherein
 R^{32} is monomethylaminophenyl or dimethylaminophenyl,
 R^{29} , R^{30} , R^{31} , R^{33} , R^{34} and R^{35} are hydrogen, and
 n is equal to zero.

31. A compound containing a radioisotope complex and having the
 Formula:



wherein:

n is equal to a number between zero and four,
 R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} and R^{35} are independently selected
 from the group consisting of:
 a. hydrogen,
 b. C_{1-4} alkylthio,

c. C_{1-4} alkylsulfonyl,

d. hydroxy,

e. C_{1-4} alkoxy,

f. NR^6R^7 , wherein

R^6 and R^7 are hydrogen or C_{1-4} alkyl,

g. phenyl(C_{1-4})alkyl,

h. C_{6-10} aryl,

i. heteroaryl,

j. heterocycle,

k. heterocycle(C_{1-4})alkyl, and

l. C_{3-6} cycloalkyl,

wherein said phenyl(C_{1-4})alkyl, C_{6-10} aryl,

heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6}

cycloalkyl is substituted with one of the following: C_{1-4}

alkylthio, C_{1-4} alkyl sulfonyl, methoxy, hydroxy,

dimethylamino or methylamino;

with the provisos that,

a) one of R^{33} through R^{35} is monoalkylaminophenyl or dialkylaminophenyl; and

b) one of R^{29} and R^{32} is selected from the group consisting of:

a. hydrogen

b. phenyl(C_{1-4})alkyl,

c. C_{6-10} aryl,

d. heteroaryl,

e. heterocycle,

f. heterocycle(C_{1-4})alkyl, and

g. C_{3-6} cycloalkyl,

wherein said phenyl(C_{1-4})alkyl, C_{6-10}

aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl is substituted with one

of the following: C_{1-4} alkylthio, C_{1-4} alkyl

sulfonyl, methoxy, hydroxy, dimethylamino or

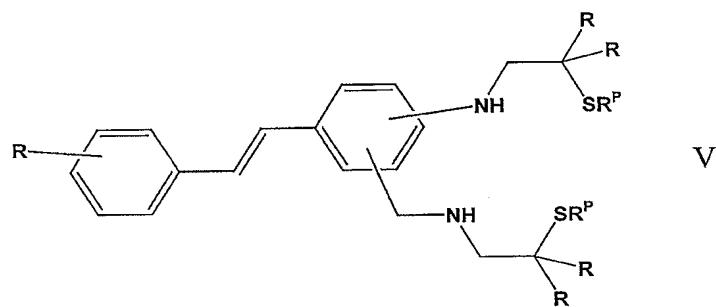
methylamino,

the other of R²⁹ and R³² represents an unsubstituted position.

32. A compound of claim 8, wherein X' is ¹⁸Fluoromethyl, ¹⁸Fluoroethyl or ¹⁸Fluoropropyl.

33. A compound of claim 16, wherein X' is ¹⁸Fluoromethyl, ¹⁸Fluoroethyl or ¹⁸Fluoropropyl.

34. A compound of general Formula V:



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of:

- a. C₁₋₄ alkylthio,
- b. halo(C₁₋₄)alkoxy,
- c. carboxy(C₁₋₅)alkyl,
- d. hydroxy,
- e. C₁₋₄ alkoxy,
- f. NR³⁶R³⁷, wherein

R³⁶ and R³⁷ are hydrogen, fluoro(C₁₋₄)alkyl or C₁₋₄ alkyl,

- g. phenyl(C₁₋₄)alkyl,
- h. C₆₋₁₀ aryl,
- i. heteroaryl,
- j. heterocycle,
- k. heterocycle(C₁₋₄)alkyl,

1. C_{3-6} cycloalkyl,

wherein said phenyl(C_{1-4})alkyl, C_{6-10} aryl, heteroaryl, heterocycle, heterocycle(C_{1-4})alkyl or C_{3-6} cycloalkyl is substituted with one of the following: C_{1-4} alkylthio, C_{1-4} alkyl sulfonyl, methoxy, hydroxy, dimethylamino or methylamino, and

m. alkyl; and

R^P is hydrogen or a sulfur protecting group.

35. A compound of claim 34, wherein said protecting group is selected from the group consisting of methoxymethyl, methoxyethoxymethyl, *p*-methoxybenzyl or benzyl.

36. A pharmaceutical composition comprising a compound of any one of claims 1-35.

37. A diagnostic composition for imaging amyloid deposits, comprising a radiolabeled compound of any one of claims 1-33; and a pharmaceutically acceptable excipient or diluent.

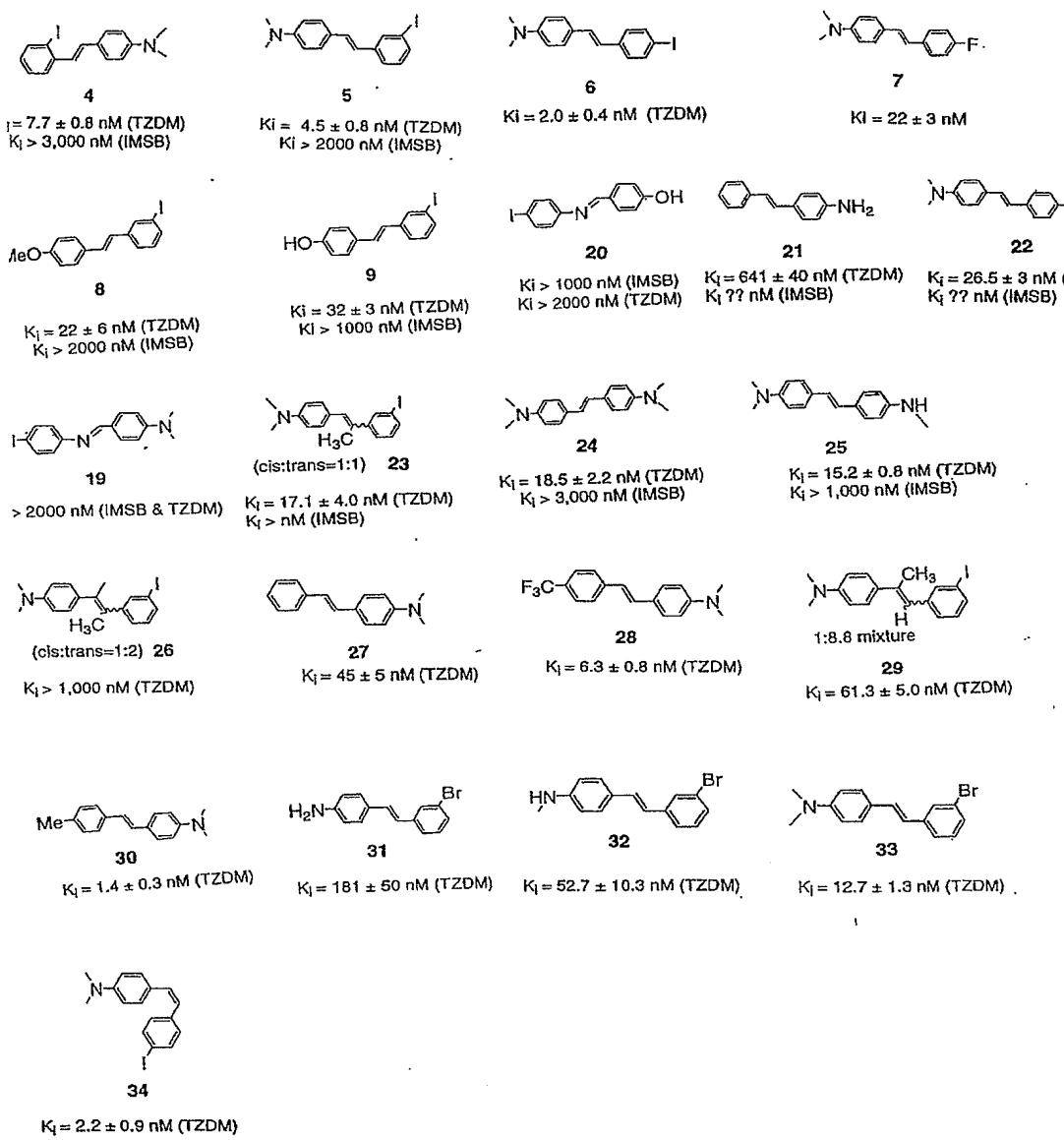
38. A method of imaging amyloid deposits, comprising:

- a. introducing into a mammal a detectable quantity of a diagnostic composition of claim 37; and
- b. allowing sufficient time for the labeled compound to be associated with amyloid deposits; and
- c. detecting the labeled compound associated with one or more amyloid deposits.

39. A method of inhibiting amyloid plaque aggregation in a mammal, comprising administering a composition of claim 36 in an amount effective to inhibit amyloid plaque aggregation.

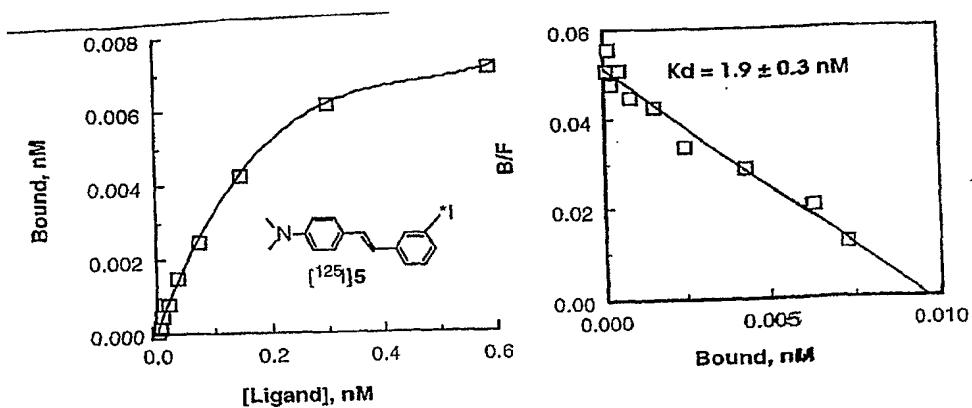
1/5

FIGURE 1



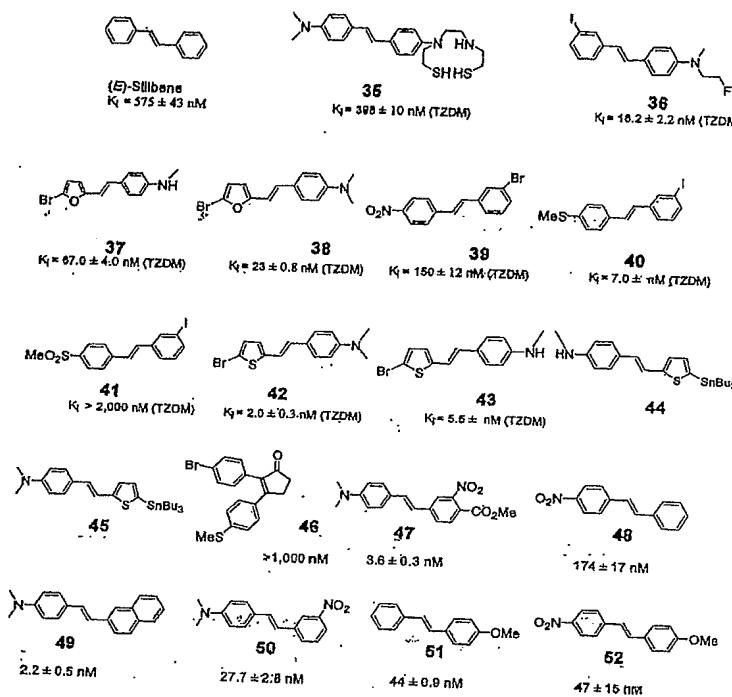
2/5

FIGURE 2



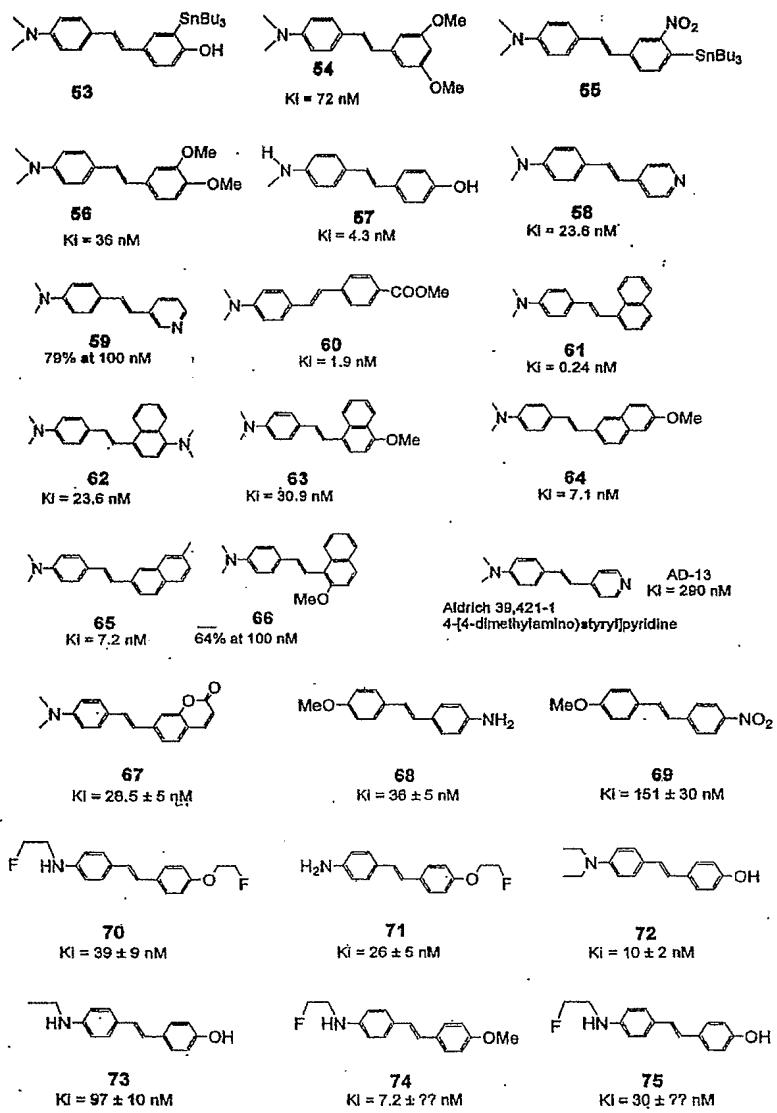
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FIGURE 3

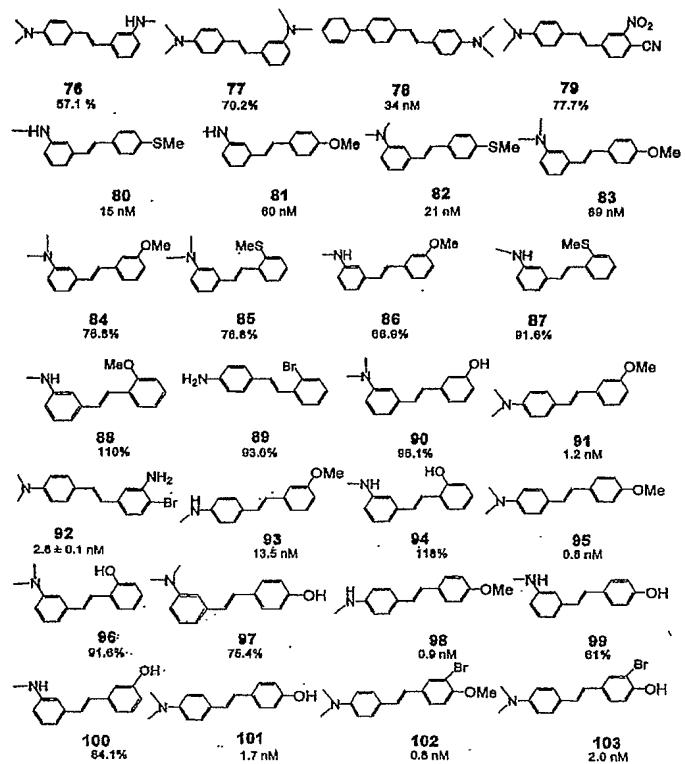


4/5

FIGURE 4



5/5
FIGURE 5



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27201

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8 (in part)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27201

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 101/00, 02
US CL : 424/1.65, 1.81, 1.85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/1.65, 1.81, 1.85

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,601,801 A (FLANAGAN et al) 11 February 1997 (11/2/1997), column 3-4.	1-8
A	Database CAPLUS on STN, Chemical abstracts, (Columbus, Ohio, USA) CA:84:73777, TEWARI et al, 'Generation and reactions of some dimethyl benzylphosphonate carbanions: synthesis of trans-diaryl-substituted ethylenes', J. Chem. Eng. Data, Vol. 21, No. 1, pages 125-131, abstract.	1-8
A	ZHAUNG et al. Radioiodinated Styrylbenzenes and Thioflavins as Probes for Amyloid Aggregates. Journal of Medicinal Chemistry, June 2001, Volume 44, pages 1905-1907.	1-8
A	LEE et al. Isomerization of (Z,Z) to (E,E)1,4-mono-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)-styrylbenzene in Strong Base: Probes for Amyloid Plaques in the Brain, Journal of Medicinal Chemistry, June 2001, Volume 44, pages 2270-2275, especially page 2271.	1-8

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	-T-	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 December 2002 (03.12.2002)

Date of mailing of the international search report

20 DEC 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Jean F. Vollano

Telephone No. 703-308-1235

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group 1, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ^{123}I or ^{125}I or ^{131}I , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl R⁴ is a non heterocyclic moiety from a, b, d, e, g, h, l.

Group 2, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl R⁴ is a non heterocyclic moiety from a, b, d, e, g, h, l.

Group 3, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{76}Br or ^{77}Br , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl R⁴ is a non heterocyclic moiety from a, b, d, e, g, h, l.

Group 4, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino R⁴ is a non heterocyclic moiety from a, b, d, e, g, h, l.

Group 5, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ^{123}I or ^{125}I or ^{131}I , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl R⁴ is a non heterocyclic moiety from a, b, c, d, e, g, h, l and at least one R¹,R², R³ or R⁴ is a carboxy alkyl group.

Group 6, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl R⁴ is a non heterocyclic moiety from a, b, c, d, e, g, h, l and at least one R¹,R², R³ or R⁴ is a carboxy alkyl group.

Group 7 , claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{76}Br or ^{77}Br , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl R⁴ is a non heterocyclic moiety from a, b, c, d, e, g, h, l and at least one R¹, R², R³ or R⁴ is a carboxy alkyl group.

Group 8 , claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl carboxy alkyl R⁴ is a non heterocyclic moiety from a, b, c, d, e, g, h, l and at least one R¹, R², R³ or R⁴ is a carboxy group.

Group 9, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ^{123}I or ^{125}I or ^{131}I , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino R⁴ is a non heterocyclic moiety from a, b, c, d, e, f, g, h, l and at least one R¹,R², R³ or R⁴ is an amine group.

Group 10, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino , R¹,R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino

INTERNATIONAL SEARCH REPORT

PCT/US02/27201

R⁴ is a non heterocyclic moiety from a, b, c, d, e, g, f, h, l and at least one R¹, R², R³ or R⁴ is an amine group.

Group 11, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ⁷⁶Br or ⁷⁷Br, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino
R⁴ is a non heterocyclic moiety from a, b, c, d, e, f, g, h, l and at least one R¹, R², R³ or R⁴ is an amine group.

Group 12, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino
R⁴ is a non heterocyclic moiety from a, b, c, d, e, f, g, h, l and at least one R¹, R², R³ or R⁴ is an amine group.

Group 13, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ¹²³I or ¹²⁵I or ¹³¹I, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l.

Group 14, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ¹⁸F, ¹⁸Fluoro alkyl amino, ¹⁸F fluoroalkyl alkylamino, R¹, R², R³ are hydrogen, alkyl, trifluoromethyl, nitro, haloalkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l.

Group 15, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ⁷⁶Br or ⁷⁷Br, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l.

Group 16, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino
R⁴ is a heterocyclic moiety from any of i, j, k, l.

Group 17, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ¹²³I or ¹²⁵I or ¹³¹I, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², R³ is a carboxy alkyl group.

Group 18, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ¹⁸F, ¹⁸Fluoro alkyl amino, ¹⁸F fluoroalkyl alkylamino, R¹, R², R³ are hydrogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is a carboxy alkyl group.

Group 19, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ⁷⁶Br or ⁷⁷Br, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is a carboxy alkyl group.

Group 20, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is a carboxy group.

Group 21, claim(s) 1-8 (in part), drawn to a compound of formula I wherein X' is ¹²³I or ¹²⁵I or ¹³¹I, R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is an amine group.

Group 22, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ¹⁸F, ¹⁸Fluoro alkyl amino, ¹⁸F fluoroalkyl alkylamino, R¹, R², R³ are hydrogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino
R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is an amine group.

INTERNATIONAL SEARCH REPORT

PCT/US02/27201

Group 23, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is ^{76}Br or ^{77}Br , R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², or R³ is an amine group.

Group 24, claim(s) 1-7 (in part), drawn to a compound of formula I wherein X' is Sn (alkyl)R¹, R², R³ are hydrogen, halogen, alkyl, trifluoromethyl, nitro, haloalkyl, carboxy alkyl or methyl amino, dimethylamino R⁴ is a heterocyclic moiety from any of i, j, k, l and at least one R¹, R², R³ or R⁴ is an amine group.

Group 25, claim(s) 1-8 (in part), drawn to a compound of formula I which is not found in any of the above groups. If this group is chosen further restriction may be required and an election of species is required.

Group 26, claim(s) 9-11 and 13-16 (in part) and 12 (in full) drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an O and X' is ^{123}I or ^{125}I or ^{131}I .

Group 27, claim(s) 9-11, and 13-15 (in part) drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an O and X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino .

Group 28, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an O and X' is ^{76}Br or ^{77}Br .

Group 29, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an O and X' is Sn (alkyl).

Group 30, claim(s) 9-11 and 13-16 (in part) drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an S and X' is ^{123}I or ^{125}I or ^{131}I .

Group 31, claim(s) 9-11, and 13-15 (in part) drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an S and X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino .

Group 32, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an S and X' is ^{76}Br or ^{77}Br .

Group 33, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an S and X' is Sn (alkyl).

Group 34, claim(s) 9-11 and 13-16 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an NR and X' is ^{123}I or ^{125}I or ^{131}I .

Group 35, claim(s) 9-11, and 13-15 (in part) drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an NR and X' is ^{18}F , ^{18}F Fluoro alkyl amino, ^{18}F fluoroalkyl alkylamino .

Group 36, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an NR and X' is ^{76}Br or ^{77}Br .

Group 37, claim(s) 9-11 and 13-15 (in part) , drawn to a heterocyclic unsaturated alkenylene aryl compound of formula II wherein the heteroatom Z is an NR and X' is Sn (alkyl).

Group 38, claim(s) 17, 21, 24 (in part) and 18 (in full) drawn to a heterocyclic diamine thio ligand of formula III wherein the heteroatom Z is an O .

Group 39, claim(s) 17, 21, 24 (in part) , and 19 (in full) drawn to a heterocyclic diamine thio ligand of formula III wherein the heteroatom Z is S .

Group 40, claim(s) 17, 20-24 (in part) , drawn to a heterocyclic diamine thio ligand of formula III wherein there is no heteroatom and Z is CR15=CR16 and R¹⁵⁻²⁵ are not heterocyclic compounds (i.e. not h, i, j or k).

Group 41, claim(s) 17, 20-24 (in part) , drawn to a heterocyclic diamine thio ligand of formula III wherein there is no heteroatom Z is CR15=CR16 and at least one or more of R¹⁵⁻²⁵ is a heterocyclic compound.

INTERNATIONAL SEARCH REPORT

PCT/US02/27201

Group 42, claim(s) 25 (in part), drawn to a technetium diamine thio radioisotope of claim 25 wherein the heteroatom Z is an O .

Group 43, claim(s) 25 (in part), drawn to a technetium diamine thio radioisotope wherein the heteroatom Z is S.

Group 44, claim(s) 25 (in part) , drawn to a technetium diamine thio radioisotope wherein there is no heteroatom and Z is CR15=CR16 and R^{15-25} are not heterocyclic compounds (i.e. not h, i, j or k).

Group 45, claim(s) 25 (in part) , drawn to a technetium diamine thio radioisotope wherein there is at least one heteroatom and Z is CR15=CR16 and R^{15-25} contain at least one heterocyclic compound.

Group 46, claim(s) 26 -30 (in part) , drawn to a phenyl dithio diamine compound of formula IV wherein there are no heterocycles R^{20-35} is a, b, c, d, e , f, g, h, k or l wherein l does not contain a heterocycle. .

Group 47, claim(s) 26-30 (in part) , drawn to a phenyl dithio diamine compound of formula wherein there is at least one heterocycle (i.e. at least one of R^{20-35} contains a heterocycle).

Group 48 , claim(s) 31 (in part) , drawn to a radioisotope complex of technetium of claim 31 wherein there is no heterocycles in the compound.

Group 49 , claim(s) 31 (in part), drawn to a radioisotope complex of technetium of claim 31 wherein there is at least one heterocycle in the compound. (i.e. at least one of R^{20-35} contains a heterocycle).

Group 50, claim(s) 34-35(in part), drawn to a compound of formula V wherein there are no heterocycles.

Group 51, claim(s) 34-35 (in part), drawn to a compound of formula V wherein there is at least one heterocycles.

It is noted that claims 32 and 33 are improperly dependent on claims 8 and 16 . Claim 32 recites X' being a ^{18}F luoromethyl etc. as does claim 33. Claims 8 and 16 recite X' being an ^{123}I and therefore the claims 32 and 33 are not proper. Since claims 36-39 depend in part on claims 32 and 33 they are also improper and are withdrawn from consideration as being non searchable.

The inventions listed as Groups 1-51 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups 1 to 25 only have a phenyl alkenylene moiety (e.g. stilbenyl moiety) to all variations. The compounds can have various heterocycles or non heterocycles and can have either radiolabeled halogen or halogen compounds or can be non radiolabeled and contain tin. The only structure in common is a phenyl alkenylene group which is not a substantial part of the molecule nor does it chemically and physically describe the properties of the compound by is common structure. Nor is the common structure applicants contribution to the art. Also there are compounds that are known in Markush group given for formula I which is shown in CA:132:4062 wherein R1 and R2 and R5 are hydrogen, X' is tri-n-butyl tin, R3 is hydrogen and R4 is from f. selection NR6R7 wherein R6 and R7 are methyl (i.e. C1-4 alkyl). For the reasons cited above including one of the compounds being known there is no special technical feature which unites the different structural groups of compounds in Groups 1-25.

Group 26-37 are drawn to structure of formula II which is not found in any of the compounds 1 to 25 and therefore there is no special technical feature which unites Groups 26-37 to Groups 1 to 25. As for any special technical feature within the compounds within Groups 26-37 there is none. The compounds all contain different heterocyclic 5 membered ring structures that are attached to a unsaturated phenyl group which is the only thing in common to all the alternatives. This is not a substantial portion of the molecule nor is it applicants contribution to the art. The different heterocyclic rings are also attached to different radiolabeled moieties or a non radiolabeled moiety and as such they are structurally different and have a lack of a special technical feature.

Groups 38-41 have a different structure that any of Groups 1-37 and don't share a special technical structural feature with the other groups since they contain a dithio, diamine linear chelating moiety and have no radiolabeled halogens or halogen compounds. Among themselves there is a 5 membered ring which can be a thieryl, or a furanyl or a phenyl which renders each member to have a structural component which gives a different physical and chemical characteristic to the group and they lack a special technical feature within the groups.

Groups 42-45 are drawn to technetium chelated compounds which are not found in any of the other compounds above. Again there is a heterocyclic moiety and variations of R groups that form multiheterocyclic compounds and multi mono heterocyclic compounds which are different structures and have different chemical and physical characteristics which are not shared by all alternatives in Groups 42-46.

Groups 46-47 are drawn to a mono phenyl diamine dithio moiety without a metal or a radiolabeled material that is not found in any of the proceeding groups. One of the two groups has heterocyclic structures and the other group does not. There can be at Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US02/27201

most 7 heterocyclic rings of varying structure which eliminates there being a special technical feature from the other group which does not have any heterocyclic rings.

Groups 48 -49 are technecium compounds that have ligands that are different from the technecium compounds in group 42-45 nor do any of the other groups have technecium as part of their structure. They lack a special technical feature with the rest of the groups. The groups themselves again differ in the heterocyclic moieties, one is without any and the other has them. This adds substantial differences in the structure.

Groups 50-51 are drawn to a non technecium, non radiolabeled stibenyl ligands which are different than the structures given above. They are divided into two groups one with heterocyclic ligands which can be up to 5 and ones without.

There is also no unity of invention within the groups since they are all drawn to different compound structures and unity of invention is directed to a compound or a compound and a method of preparing the compound or a compound and a method of preparing the compound and a method of use of the compound etc. These groupings do not fit any of the groups above and therefore they lack unity of invention.

Continuation of B. FIELDS SEARCHED Item 3:
EAST, CAS ONLINE, BEILSTEIN

search term: structure drawing , 123I, 125I, 131I, radiolabeled, neurodegenerative disorder